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PRIMARY SYSTEMIC AMYLOIDOSIS

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PRIMARY systemic amyloidosis, as classified by Lubarsch in 1929,[1] is characterized by involvement of the cardiovascular system and tissues of mesodermal origin in the absence of chronic illness.

In 1939 Koletsky and Stecher[2] reviewed 23 cases of primary systemic amyloidosis. In 1945 Lindsay and Knorp[3] identified 40 cases in the literature. Since 1944 Golden[4] and Soisalo and Ritama[5] have added 2 cases, bringing the total to 42.

Two more cases are now reported, not only because of the extreme rarity of this disease but also because of the interesting anatomic changes observed in each.

REPORT OF CASES

CASE 1.—A 63 year old white married man entered the hospital six days before his death. He complained that he had had swelling of the ankles for eighteen months. His illness began at the age of 58. At that time he consulted his physician because of a "run down" feeling. Albuminuria was discovered, and the patient was restricted to a low salt, low fat diet. His diet was said to be free of rich food and "basic nutrients." One and one-half years before death he began to lose weight, became short of breath and noted edema of the ankles. His systolic blood pressure at that time was 180 mm. of mercury. Small xanthoma-like nodules appeared in his eyelids. Six months before his death the patient noted difficulty in swallowing solids and, later, fluids. His voice became hoarse.

On admission the patient appeared to be a poorly developed, emaciated white man with severe kyphoscoliosis and acute respiratory distress. There was marked pitting edema of the extremities and the scrotum. The skin was loose, atrophic and inelastic. Petechiae were scattered over the eyelids, the forearms, the gums, the scrotum and the legs. There was enlargement with limitation of movement of the joints. The teeth were carious, and the gums showed marked pyorrhea. Glossitis and papillary atrophy of the tongue were noted. The thyroid cartilage was ossified. There were marked pulmonary edema and bilateral hydrothorax.

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1. Lubarsch, O.: Virchows Arch. f. path. Anat. **271**:867, 1929.
2. Koletsky, S., and Stecher, R. M.: Arch. Path. **27**:267, 1939.
3. Lindsay, S., and Knorp, W. F.: Arch. Path. **39**:315, 1945.
4. Golden, A.: Arch. Int. Med. **75**:413, 1945.
5. Soisalo, P., and Ritama, V.: Acta med. Scandinav. **116**:260, 1944.

The heart was enlarged, the rhythm was irregular, and a soft systolic murmur was heard over the entire precordium. Electrocardiograms indicated myocardial disease. The prostate gland was slightly enlarged.

Accessory clinical data are presented in table 1.

Postmortem Examination (twenty hours after death).—In addition to the superficial changes observed before death, small nodules could be seen on the under surface of the tongue and the epiglottis.

TABLE 1.—*Accessory Clinical Data*

		Case 1	Case 2
Urine	Albumin	3+, or 19 Gm. per liter of 24 hr. specimen	3+
	Specific gravity	1.021	
	Microscopic observations	3-5 white blood cells; hyaline casts	2 or 3 white blood cells; occasional red blood cell; hyaline and granular casts
	Bence Jones protein	.....	Negative
Blood	Sedimentation rate (corrected)	26 mm. in 1 hr.	40 mm. in 1 hr.
	Hemoglobin	10 Gm. per 100 cc.	10 Gm. per 100 cc.
	Erythrocytes	2,800,000	2,970,000
	Hematocrit	38	33
	Color index	1.1	1.08
	Mean corpuscular volume	135	110
	Mean corpuscular hemoglobin concentration	36	34
	Leukocyte count	12,300	18,200
	Prothrombin time	23 seconds (control 29)	
Serologic tests	Kline	Negative	Negative
	Mazzini	Negative	Negative
Blood chemistry	Nonprotein nitrogen	43 mg. per 100 cc.	68 mg. per 100 cc.
	Urea nitrogen	24.2	46.5
	Urea ratio	56.2	68.3
	Uric acid	.....	8.3
	Calcium	9.6	16.5
	Phosphorus	3.1	5.1
	Total protein	5.2	7.1
	Albumin	2.7	2.9
	Globulin	2.5	4.2
	A/G ratio	1.1	0.69
	Chlorides	580	512
	Carbon dioxide-combining power	.....	57 vol. per cent
	Cholesterol	320	
Tuberculin test		Negative	
Liver function	Sulfobromophthalein sodium test	.....	3 per cent retention after 5 min.; 0 after 46 min.

The most remarkable alterations were noted in the deposits of body fat and in the small blood vessels. The subcutaneous and the perirenal fat were decreased in amount, were normally soft and lobulated, and had the dark yellow color seen often in patients who have been chronically ill. In contrast to this, the appendices epiploicae were gray and of such resiliency that they projected almost perpendicularly from the intestinal surface. The mesenteric fat presented a similar appearance, and the consistency of serosal fat lining portions of the gastrointestinal tract lent a peculiar rigidity to these structures. In many of these areas the surface was spotted by tiny grayish white flecks resembling miliary granuloma or fat necrosis (fig. 4).

The omentum consisted of only a filmy membrane, in which was seen sparse grayish fat, each lobule being very small. This afforded even greater contrast to the radiating arteries and veins, the walls of which were so rigid that on sectioning them one received an impression of cutting such material as tracheal rings.

The abdominal and thoracic cavities contained 500 to 1,000 cc. of clear yellow fluid.

The heart weighed 410 Gm. All chambers were markedly dilated. The myocardium was soft and flabby. The endocardium, especially that of the left auricle and the mitral valve, was slightly and diffusely thickened. There was moderate coronary arteriosclerosis, as well as advanced but not extreme aortic arteriosclerosis (fig. 1).

The right and left lungs weighed 1,400 Gm. and 1,000 Gm., respectively. Except for a healed reinfection type tuberculous lesion of the apex of the right lung, both lungs were similar in appearance. They were extremely boggy, and large amounts of fluid poured from the severed bronchi. The tiny branches of the pulmonary vessels presented the same peculiar rigidity noted in all of the abdominal vessels. Moreover, the alveolar walls were also slightly rigid, having a waxy, honeycomb appearance (fig. 3).

The mucous membrane of the gastrointestinal tract was grossly atrophic, but edematous. Small areas of hemorrhagic necrosis were frequent. A 0.5 cm. ulcer with indurated and sharp borders was present in the pyloric region of the stomach and in the fundus (fig. 2). An extensive area of fresh necrosis and recent ulceration was seen at the site of impacted fecal material in the lower part of the rectum.

The liver, the biliary tract, the pancreas, the spleen and the adrenal glands showed no unusual gross changes.

The kidneys weighed 170 Gm. each. The surface was rough, and on sectioning the diminution in size was seen to be due to a diffuse uniform contraction of the most peripheral portion of the cortex (fig. 5).

Other changes in the genitourinary tract were: chronic cystitis and urethritis, atrophy of the right testicle and moderate nodular hyperplasia of the prostate.

The voluntary muscles were flabby and atrophic. Joint capsules, when noted, were thickened, as was the periosteum of ribs and sternum. The marrow was gelatinous in consistency, and the trabeculae were unusually thin and brittle.

The brain and the meninges showed no anatomic alterations.

Microscopic Examination.—The most dramatic reaction was seen in the walls of small veins and arteries throughout the body (figs. 6 and 8). Amorphous masses of eosinophilic material replaced the media and the adventitia of these vessels. This was distributed unevenly so that cross sections showed the walls to be of irregular width. Usually the intima was spared but greatly swollen by accumulation of fat, which stained bright red with scarlet red, in clear distinction from the hazy pink of the adjacent media. Occasionally giant cells were found at the periphery of the masses of pink-staining material which proved to be amyloid. In the liver and the spleen the small arterioles showed similar changes, but these were not so extreme. Without the aid of amyloid stains they could have been interpreted in some areas as extreme hyaline arteriolosclerosis or fibrinoid necrosis.

Vessels of capillary caliber were often made clearly visible by a wavy pink ribbon of amyloid underlining the endothelium. Larger vessels, such as the celiac, renal and coronary arteries and the aorta, showed arteriosclerosis but no extensive amyloid change. Fuzzy dark masses in the intima and the media of these vessels occasionally stained positively for amyloid. Cerebral vessels were unaltered.

The vessels most affected were those of the skin, the tongue, the skeletal muscle, the respiratory tract, the heart, fat and the gastrointestinal and genitourinary

Fig. 1. (case 1).—Heart. Note arteriosclerosis of the large coronary vessels. Amyloid alteration of the myocardium is a factor in the extreme cardiac dilatation.

Fig. 2 (case 1).—Stomach. Note the atrophic gastric mucosa and the small ulcer at the site of large submucosal deposits of amyloid.

Fig. 3 (case 1).—Lung. Note the prominence of alveolar septums and the patency of small vessels on the cut surface of the lung. Microscopic sections showed these changes to be due to amyloid.

Fig. 4 (case 1).—Large intestine. This shows the peculiar rigid appendices epiploicae which lined the entire large intestine. Note the tortuous, thickened veins and arteries.

Fig. 5 (case 1).—Kidneys. Note contraction of the peripheral cortex due to hyaline and amyloid alteration of glomeruli. The thickening of vessel walls is clearly shown.

tracts. The vessels of the endocrine organs, the abdominal viscera and the brain were slightly or not at all changed.

Tissues of special interest were as follows:

Skin: In the small xanthoma-like nodule of the eyelid the preexisting connective tissue or fat had been completely replaced by homogeneous pink-staining granular material. The epithelium overlying this mass of amyloid was atrophic, and the dermal appendages were either absent or atrophic. In some areas the vessels were greatly thickened by hyalin-like material which stained with congo red.

Fat: Fat, such as subcutaneous or perirenal fat, which was grossly not of unusual appearance, was proved by microscopic section to consist of fetal fat, through which coursed vessels occasionally altered by deposition of amyloid. The membrane of the individual fat cell was often sharply delineated because of a bright pink thickening. In other areas this was more pronounced, and the adjacent fat cells seemed to be cemented together by the eosinophilic substance. The most advanced changes were seen in the appendices epiploicae and the mesentery, where remained only globules of neutral fat, dotting the large honeycomb of amyloid (fig. 8).

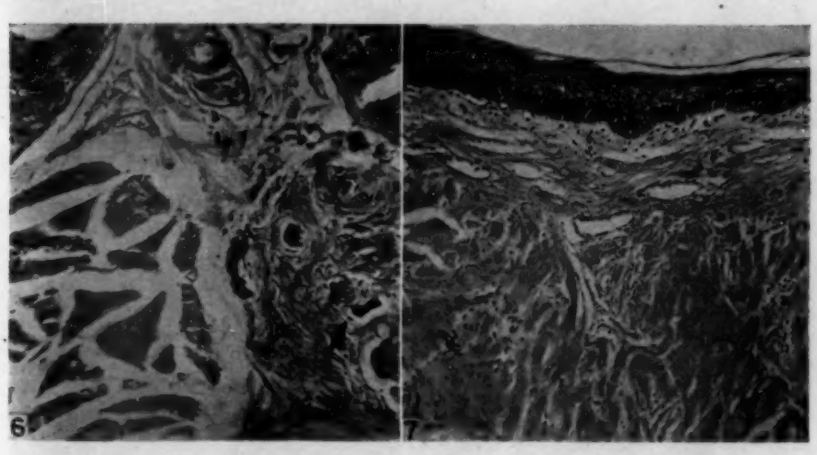

Fig. 6 (case 1).—Tongue; congo red stain; × 95. The vascular thickening is due to irregular accumulations of amyloid in the media and the adventitia. The arrow indicates a giant cell in the center of the largest mass. Amyloid was seen within muscle fibers in adjacent areas.

Fig. 7 (case 1).—Tongue; congo red stain; × 95. The opalescent waxy nodule on the under surface of the tongue is shown to be composed of masses of amyloid. Note atrophy of epithelium. The appearance of the skin was similar.

In this fat the inflammatory reaction which was seen in other sections throughout the body was more prominent. It consisted of lymphocytes, mononuclear cells and large reticuloendothelial cells. The last were sometimes of gigantic proportions, their cytoplasm containing inclusions of amyloid. An occasional cell appeared to be dying, its nucleus having disappeared; instead remained only a cell membrane enclosing several globules of amyloid (fig. 12). Such areas as these apparently represented the miliary nodules noted grossly. In addition, giant cells of the foreign body type surrounded accumulations of amyloid, whether in fat or in blood vessels (fig. 8). At the periphery of one such mass in the mesenteric fat was a thin rim of mature bone in which could be seen cells resembling osteocytes (fig. 10).

Tongue: The grossly small opalescent waxy mass on the under surface of the tongue was composed almost entirely of amorphous pink-staining material, through which were scattered the remains of cells resembling fibroblasts or mononuclear cells (fig. 7).

At the periphery the larger mass merged with a narrow band of amyloid that was replacing the papillary connective tissue and contrasting remarkably with the

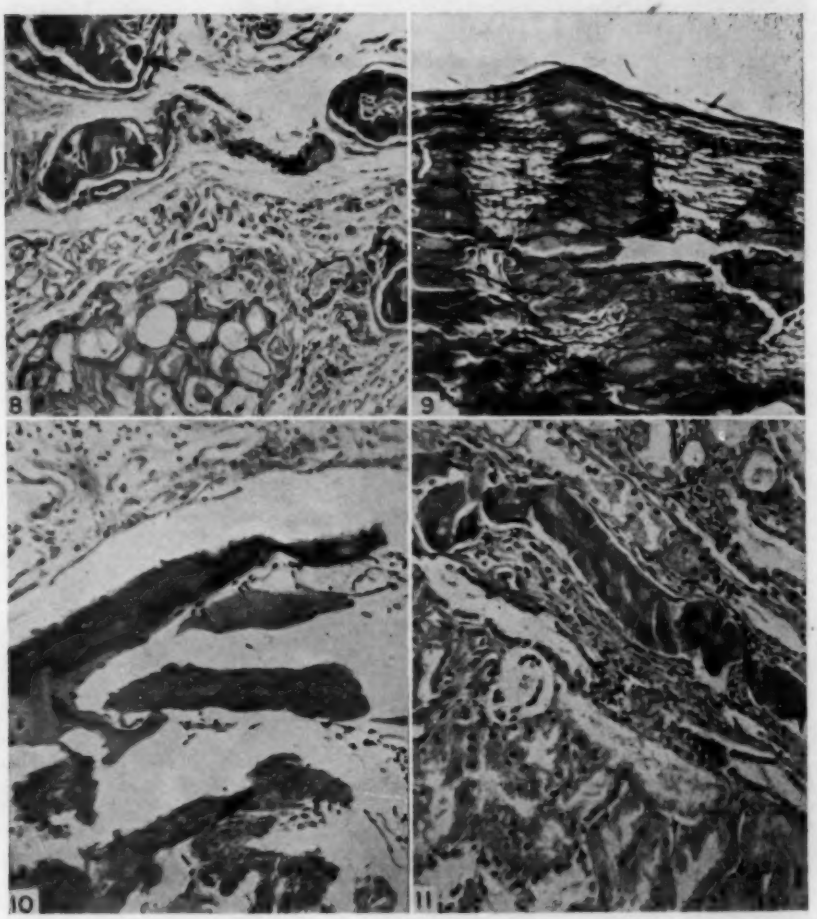

Fig. 8 (case 1).—Appendices epiploica; hematoxylin and eosin; × 99. Note globular masses of amyloid in vessel walls. An arrow indicates an accompanying giant cell reaction. Adjacent fat cells are altered by amyloid deposited on the cell membranes, sharply outlining sites of neutral fat.

Fig. 9 (case 1).—Left auricle of heart; Verhoeff–Van Gieson stain; × 141.5. The density of the globular parallel columns of amyloid is demonstrated by the compression of connective tissue and the fragmentation of elastic fibrils.

Fig. 10 (case 1).—Mesentery; hematoxylin and eosin; × 141.5. At the periphery of a mass of amyloid is seen a small segment of bone. Note the adjacent inflammatory reaction.

Fig. 11 (case 1).—Kidney; congo red stain; × 141.5. The hard laminated cast, which has stained positively for amyloid, is accompanied by a giant cell reaction similar to that seen in Bence Jones proteinuria. Note atrophy of tubular epithelium.

overlying layer of atrophic epithelium. Small extensions of the subepithelial amyloid were confluent with large globular masses of this substance in nearby vascular walls (fig. 6).

Many of the cells of both tongue and skeletal muscle were atrophic. In some areas fibrosis was prominent. In addition, numerous fibers showed occasional almost nodular swellings. Striations were no longer visible within these, and the swellings stained with congo red.

Respiratory Tract: Small masses of amyloid were located beneath the epithelium of the vocal cords. The alveolar walls of the lungs were thickened with hyalin-like material, which was sometimes distributed diffusely but as often was localized in nodules to portions of the septums. The latter projected at times on thin stalks into the alveoli, where they occasionally were surrounded by giant cells. Fluid, fibrin and macrophages containing pigment or droplets of amyloid filled the alveoli.

The small cavity at the apex of the right lung was completely epithelized; but here, because of the fibrous adhesions containing large blood vessels, there was a concentration of amyloid in proportionate excess to that seen in other parts of the lungs.

Heart: The amyloid was layered in strips beneath the endothelium. In the left auricle, however, perpendicular columns extended across the endocardium, these masses paralleling each other at more or less regular intervals (fig. 9). In the coronary vessels the amyloid change continued down into the branches within the myocardium, so that focal masses of amyloid were seen separating muscle cells. The myocardium was vacuolated with moderate accumulations of fat. Focal myocardial necrosis and fibrosis were seen. Sheets of amyloid replaced the epicardium in some areas.

Gastrointestinal Tract: The mucosa of the stomach, like that of the esophagus, was atrophic. At the site of the ulcer the muscularis mucosae and the submucosa were fused into a dense eosinophilic mass. Here the substance resembled the traditional molten wax, seeping into the crevices of the surrounding tissue and gradually merging with normal structures well to the periphery. The smooth muscle at the base of the ulcer was transformed into amyloid, and small nodular accumulations were also found subserosally.

Consistently found throughout the entire gastrointestinal tract were: atrophic mucosa; large pink vessels swollen with infiltrations of amyloid; altered muscle; occasional subperitoneal masses of amyloid.

Genitourinary Tract: Congo red stains showed the thickened renal capsule to be spotted with round, bright red masses representing amyloid-altered blood vessels. At the pelvis the large vessels also contained amyloid, and their small branches within the renal parenchyma still retained the features characteristic of the amyloid change.

Uniform and diffuse scarring of the peripheral cortex was accompanied by interstitial fibrosis and mononuclear and lymphocytic inflammatory reaction. Hyalin-like thickening of the basement membrane, rarely due to amyloid, occurred throughout the proximal nephron. Many of the glomerular tufts were hyalinized, and some were adherent to the surrounding capsule, which was usually thickened by hyaline or fibrous change. Some of the glomeruli stained positive for amyloid, but the ambiguous staining of the majority prompted the interpretation that the degenerative changes were secondary to amyloid alteration of the vessels. The glomeruli deep in the cortex were not unusual.

Most prominent of the many casts within the renal tubules was the rare waxy laminated cast, which stained brilliantly in the congo red preparation (fig. 11). Proof of the unusual consistency of these casts was the accompanying giant cell

reaction, similar to that seen in Bence Jones proteinuria. These changes were associated with fatty alteration and degeneration of tubular epithelium.

Atrophy of epithelium, chronic inflammation and vascular amyloid change characterized the remainder of the urinary tract.

Bones and Joints: Ribs, sternum, femur and vertebrae were examined. Sections of the sternum and the ribs were framed by a thick rim of periosteal amyloid. Portions of the cartilage likewise were replaced by material reacting positively with congo red. The trabeculae were greatly thinned, and the marrow in some areas was gelatinous. Except for that in occasional small vessels, no amyloid change was seen within the bone.

CASE 2.—An obese white woman 52 years of age entered the hospital four days before her death. She complained of recent diarrhea and progressively severe arthritis of one year's duration. This was accompanied by anorexia, frequent bouts of nausea and vomiting with hematemesis, and loss of weight. Three months prior to death her tongue became beefy red and sore.

Her past history was uneventful except for mild systolic hypertension, noted at the age of 42, and exertional dyspnea, together with precordial pain, for three years prior to death. Her diet was said to be deficient in protein and green vegetables.

On admission she showed evidence of loss of weight and pallor. There was marked limitation of movement of the jaws, the elbows, the shoulders and the knees; the latter were swollen and contained fluid. Moderate thoracic kyphosis was noted. Roentgenograms of the left knee showed extensive osteoporosis of the lower part of the femur and the upper part of the tibia. There was atrophy of the muscles of the shoulders and the calves. A 0.5 cm. nodule was palpated in the subcutaneous tissue of the left wrist. There were reddening and atrophy of the anterior part of the tongue. The trachea was firm and indurated, but no definite mass was felt. Rales were auscultated at the base of the right lung. The cardiovascular system revealed tortuosity and silvering of retinal vessels, apparent cardiac enlargement, frequent extrasystoles, a soft systolic murmur, which was heard over the entire precordium, and a blood pressure of 165 systolic and 80 diastolic.

Accessory clinical data are presented in table 1.

On the third hospital day the patient's nausea became definitely worse. She could retain nothing by mouth. In spite of the administration of penicillin, her temperature rose to 39 C. (100.4 F.), and she became comatose. She died on the fourth hospital day, after an episode of vomiting.

The final clinical diagnosis was: rheumatoid arthritis, "ertron" (a high potency vitamin D preparation) poisoning with renal insufficiency, aspiration pneumonia.

Postmortem Examination (ten hours after death; limited to a 6-inch [15 cm.] abdominal incision).—The external examination confirmed the observations made clinically

The thoracic cavity contained no free fluid. The left lung weighed 450 Gm. and the right 580 Gm. The lower lobe of the latter was marked by several areas of consolidation.

The heart was not hypertrophied. Epicardial thickening was noted in several areas. The mitral and aortic valves were greatly thickened, as were several chordae tendineae. Calcification of the base of the aortic cusps was striking. No coronary or aortic arteriosclerosis was noted.

There was no free peritoneal fluid. The serosal intestinal surfaces were spotted by tiny petechial hemorrhages. The esophagus was almost completely obstructed by edema of the submucosa. The stomach was greatly distended with fluid, and

the mucosa markedly hemorrhagic and edematous. The liver was enlarged, weighing 2,660 Gm., and pale. The spleen, normal in size, was soft, mushy and gray. The left and right kidneys weighed 165 and 140 Gm., respectively. They showed no gross alterations except for retention cysts of varying size in the left kidney. The uterus and ovaries were atrophic.

No other gross changes were noted.

Microscopic Examination.—The most interesting microscopic changes were seen in the heart, the lungs and the intestines.

The pericardium was replaced almost completely by irregular, confluent masses of amyloid, through which were scattered numerous bizarre giant cells. Some of the giant cells consisted only of clusters of nuclei. In some the cytoplasm was plainly visible and contained droplets of material which stained positively for amyloid; in others the cytoplasmic outlines were indistinguishable from adjacent amyloid substance (fig. 13).

Individual myocardial fibers were definitely altered by the amyloid process. In the hematoxylin and eosin preparations these changes resembled Zenker's degeneration of voluntary muscle; however, the dark intrafibrillar swellings stained with congo red. Myocardial fibrosis, fatty alteration and fragmentation of fibers were also prominent. Occasional masses of amyloid were present in the interstitial tissue of the heart. They often appeared to represent tangential cuts at the periphery of blood vessels, most of which were altered by the deposition of amyloid. There was diffuse hyaline thickening of the endocardium, as well as nodular accumulations of amyloid material.

In the lung, the alveolar septums showed bright pink nodular masses which retained amyloid stains (fig. 14). These swellings projected into the alveolar lumens and were there rarely surrounded by giant cells of the foreign body type. Few capillaries were involved by amyloid changes. There were focal atelectasis and lobular pneumonia in the lower lobe of the right lung.

The submucosa of the entire esophagus was greatly edematous, and the mucosa somewhat atrophic. The lower third of the esophagus showed most dramatic changes. Here the normal structure of the inner muscular layer was completely lost. Instead one saw a disorderly array of deeply staining swollen fibers fused together, and at the periphery of these areas, tiny granular changes within less altered fibers. Huge giant cells, some of them with hundreds of nuclei, were abundantly scattered through the amorphous mass of pink material, which stained positively for amyloid. Except for the compact chromatin of their nuclei, these giant cells were similar to those sometimes seen in regenerating voluntary muscle. The adjacent layers of muscle showed less extensive changes and smaller giant cells, some of which resembled Aschoff cells (fig. 15).

Similar changes were seen in the muscle of the stomach and small intestine. Here, too, the mucosa was uniformly atrophic and the submucosal vessels were irregularly thickened by the pink-staining nodular masses of amyloid. In the rectum the presence of giant cells was not outstanding.

The hepatomegaly was seen to be due to extensive formation of blood in the sinusoids and portal spaces. Hepatic parenchymal cells contained both fat and glycogen. There were many islands of blood formation and abundant iron pigment in the spleen. Some of the splenic arterioles showed a faintly positive stain for amyloid; most, however, showed mere hyaline thickening.

The renal epithelium was swollen, and albuminous casts outlined the tubular lumens. The small arteries and arterioles were thickened, but only rare vessels stained positively for amyloid. There was some interstitial fibrosis in areas where glomeruli were atrophic.

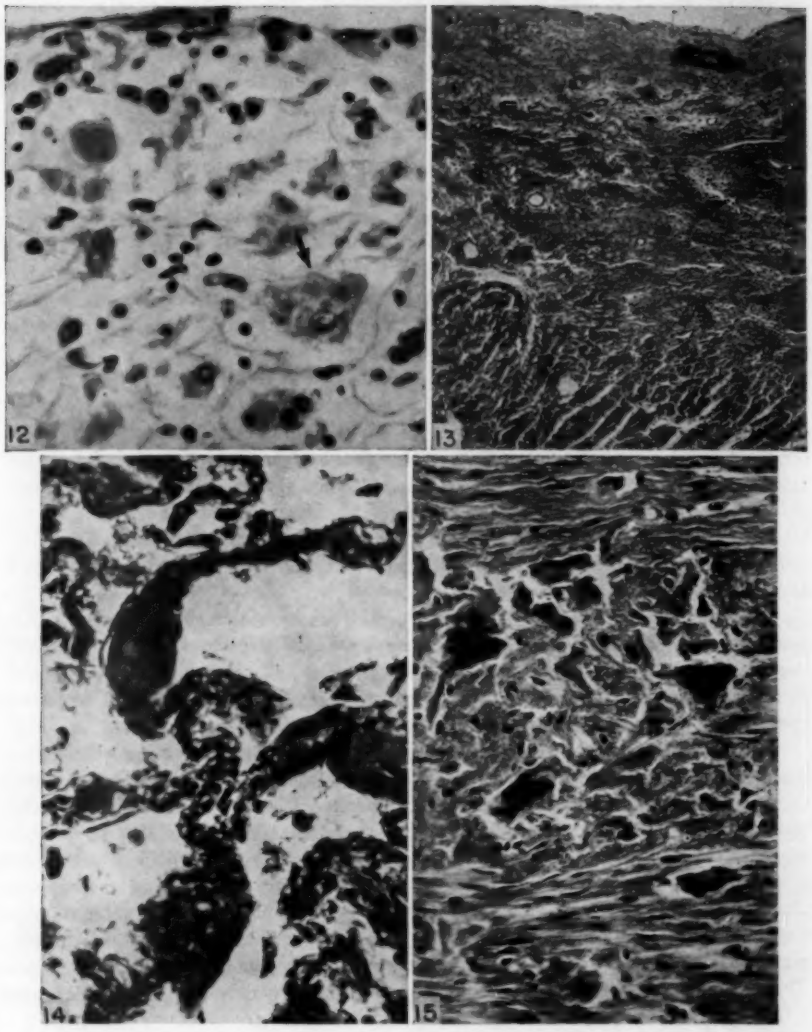

Fig. 12 (case 1).—Mesenteric fat; congo red stain; × 495.5. Large reticuloendothelial cells containing droplets of congo red–staining material are seen. This inflammatory reaction is at the periphery of a mass of amyloid not shown in the photograph.

Fig. 13 (case 2).—Heart; hematoxylin and eosin; × 35. Note the thickening of the epicardium due to massive accumulations of amyloid, through which are seen many giant cells of varying size and shape. The increased density of vessels due to amyloid alteration is shown.

Fig. 14 (case 2).—Lung; hematoxylin and eosin; × 283. The dark nodular swellings in alveolar septums have taken a stain for amyloid.

Fig. 15 (case 2).—Esophagus; hematoxylin and eosin; × 495.5. Note the bizarre giant cells associated with amyloid alteration of smooth muscle. Other portions of the gastrointestinal tract were similar.

The uterus, tubes and ovaries reflected the influence of postmenopausal changes. Some of the smaller vessels in the ovary stained brilliantly with congo red. The vaginal mucosa was extremely atrophic.

COMMENT

Clinical Findings.—Accurate classification of cases of amyloidosis is difficult.[6] Although some cases of secondary amyloidosis may show only the classic involvement of liver, spleen, kidney and adrenal gland, others show vascular involvement also, and symptoms resulting therefrom. Autopsy may reveal that vessels are affected to some extent throughout the entire body in cases classified clinically as instances of tumor-forming amyloidosis, the tumors being due to large amounts of amyloid deposited locally in the skin, the tongue and the respiratory, gastrointestinal and urinary tracts. Similarly, primary systemic amyloidosis may occur with massive deposits in one place as in tumor-forming amyloidosis, or occasional involvement of liver, spleen, kidneys or adrenal glands as in secondary amyloidosis.

A second difficulty arises in the clinical diagnosis of primary systemic amyloidosis in that this disorder, like other generalized diseases, may be associated with a variety of symptoms, according to the systems affected. Although many systems were involved in both the cases recorded here, the cardiac changes in case 1 eclipsed other aspects of the case, and in case 2 the symptoms referable to involvement of the joints and the gastrointestinal signs were predominant. The 2 cases, however, are typical in that they present diagnostic problems of interest to practitioners of almost every medical specialty.

Skin: Eight of 24 cases in the series reviewed by Koletsky and Stecher [2] showed cutaneous involvement. Even in the absence of definite amyloid tumors, the skin itself may be diffusely atrophic, giving the appearance of scleroderma. This atrophy may be related to vascular deposits, as well as to the avitaminosis which is often associated with extensive amyloid involvement of the gastrointestinal tract. In case 1 small xanthoma-like tumors of the eyelids developed, the nodular and waxy appearance of which was due to masses of amyloid deposited in the corium.

Blood: Probably because of the vascular damage, petechiae are a frequent finding in the skin and the mucous membranes.[2] The atrophy of the gastric mucosa is of special interest in relation to the macrocytic anemias seen in both of the cases reported here.

Oral Cavity and Upper Respiratory Tract: In both cases questionable masses were palpated in the trachea. In case 1 this finding, together with hoarseness, influenced a tentative diagnosis of carcinoma of the

6. Reimann, H. A.; Koucky, R. F., and Eklund, C. M.: Am. J. Path. **11**: 977, 1935.

larynx. In case 2 the diagnosis of carcinoma was briefly entertained because of a small ulcer of the tongue. In both cases there were pronounced glossitis and atrophy of the tongue, a frequent finding not only in anemias and avitaminosis but also in primary systemic amyloidosis. The amyloid deposited in the vessels and the tissues adjacent to these structures offers adequate explanation for the confusing array of clinical signs and symptoms. These findings have been reported in previous cases [7] of primary systemic amyloidosis. Ellenberg [8] described atrophy of the tongue responding to thiamine hydrochloride in a case of secondary amyloidosis with involvement of blood vessels.

Gastrointestinal Tract: Generalized atrophy of the mucous membranes (fig. 2) and involvement of muscle may lead to improper absorption and difficulty of swallowing with consequent improper intake of food. A host of metabolic disorders may result. These may be manifested clinically by loss of weight, edema, glossitis, macrocytic anemia, scleroderma, etc.

In addition, ulcers incident to large submucosal accumulations of amyloid may serve to confuse the surgeon as he seeks to determine the cause of abdominal pain, hematemesis, melena, constipation or diarrhea. Lubarsch and Borchardt [9] focused attention on these gastric ulcers. Several such ulcers were seen in case 1 (fig. 2).

Skeletal System: Arthritis has long been known as a possible etiologic factor in cases of secondary amyloidosis.[10] In cases of primary systemic amyloidosis the reverse is true. Extensive amyloid deposits occur in synovial membranes, periosteum and perichondrium. Swelling, immobility and pain result. In addition, probably secondary to some other metabolic change, osteoporosis develops, which may not appear consistently related to blood calcium and phosphorus determinations (table 1).

Cardiovascular System: The most outstanding feature of these cases and those previously reported is the change observed in the blood vessels throughout the entire body, especially in tissues of mesodermal origin. In 95 per cent of the cases reported by Koletsky and Stecher [2] the heart was involved by deposition of varying amounts of amyloid. The endocardial and myocardial involvement may result in murmurs, electrocardiographic changes, cardiac dilatation and pulmonary and generalized edema (fig. 1).

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7. Spain, D. M., and Barrett, R. C.: Arch. Path. **38**:203, 1944

8. Ellenberg, M.: J. Mt. Sinai Hosp. **10**:323, 1943.

9. Lubarsch, O., and Borchardt, H., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 4, pt. 3.

10. Trasoff, A.; Schneeberg, N., and Scarf, M.: Arch. Int. Med. **74**:4, 1944.

Genitourinary Tract: This tract is the one most commonly affected by local deposition of amyloid. It is also of principal interest in cases of secondary amyloidosis, because of the glomerular changes.[11] However, renal symptoms are inconspicuous in cases of primary systemic amyloidosis. In 6 of the cases reviewed by us [12] the symptoms, as in our case 2, were due only to arteriolonephrosclerosis and, in 1 case, to pyelonephritis. Larsen,[12i] Gerber,[12q] Soisalo and Ritama [5] and Perla and Gross [12s] reported cases more similar to case 1, in which there was amyloid alteration of vessels, some glomeruli and an occasional tubular basement membrane (fig. 5). In the remaining 8 cases in which changes were seen in the kidney they consisted only of slight amyloid alteration of vessels, cloudy swelling or presence of casts. These findings suggest that in rare instances of primary systemic amyloidosis the renal symptoms may be similar to those in cases of secondary amyloidosis; in most instances, however, the clinical signs are secondary to hyaline arteriolar disease or to slight renal vascular amyloidosis.

Pathologic Anatomy.—In cases of primary systemic amyloidosis the anatomic changes are even more varied than the clinical symptoms. The general appearance and the distribution of the lesions described in the present case reports are quite representative of those recorded in other cases. However, these 2 cases serve to focus attention on certain morphologic features not emphasized in previous reviews of primary systemic amyloidosis:

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11. Rosenblatt, M. B.: Am. J. M. Sc. **186**:558, 1933.

12. (*a*) Wild, C.: Beitr. z. path. Anat. u. z. allg. Path. **1**:177, 1886. (*b*) Steinhaus, F.: Ztschr. f. klin. Med. **45**:375, 1902 (*c*) Beneke, R., and Bonning, F.: Beitr. z. path. Anat. u. z. allg. Path. **44**:362, 1908. (*d*) Ritter, E.: Virchows Arch. f. path. Anat. **192**:536, 1908. (*e*) Beneke, R.: Centralbl. f. allg. Path. u. path. Anat. **33**:240, 1922. (*f*) Königstein, H.: Arch. f. Dermat. u. Syph. **148**: 330, 1925. (*g*) Silwer, H., and Lindblom, A. E.: Acta med. Scandinav. **64**:529, 1926. (*h*) Lubarsch.[1] (*i*) Larsen, R. M.: Am. J. Path. **6**:147, 1930. (*j*) Warren, S.: ibid. **6**:161, 1930. (*k*) Pick, L.: Klin. Wchnschr. **10**:1515, 1931. (*l*) Mollow, W., and Lebell: Wien. Arch. f. inn. Med. **22**:205, 1932. (*m*) Koller, F.: Schweiz. med. Wchnschr. **62**:522, 1932. (*n*) Gerstel, G.: Virchows Arch. f. path. Anat. **283**:466, 1932. (*o*) Gottron, H.: Arch. f. Dermat. u. Syph. **166**:584, 1932. (*p*) Strauss, A.: Virchows Arch. f. path. Anat. **291**:219, 1933. (*q*) Gerber, I. E.: Arch. Path. **17**:620, 1934. (*r*) Michelson, H. E., and Lynch, F. W.: Arch. Dermat. & Syph. **29**:805, 1934. (*s*) Perla, D., and Gross, H.: Am. J. Path. **11**:93, 1935. (*t*) Reimann, Koucky and Eklund.[6] (*u*) Ferris, H. W.: Am. J. Path. **12**:701, 1936. (*v*) Kerwin, A. J.: J. Lab. & Clin. Med. **22**:255, 1936. (*w*) Weber, F. P.; Cade, S.; Stott, A. W., and Pulvertaft, R. J. V.: Quart. J. Med. **6**:181, 1937. (*x*) DeNavasquez, D., and Treble, H. A.: Brain **61**:116, 1938. (y) Koletsky and Stecher.[2] (*z*) Binford, C. H.: Arch. Path. **29**:314, 1940. (*a'*) Götze, W., and Krucke, W.: Arch. f. Psychiat. **114**:183, 1941. (*b'*) Pearson, B.; Rice, M. M., and Dickens, K. la V.: Arch. Path. **32**:1, 1941. (*c'*) Sappington, S. W.; Davie, J. H., and Horneff, J. A.: J. Lab. & Clin. Med. **27**:882, 1942. (*d'*) Spain and Barrett.[7] (*e'*) Soisalo and Ritama.[5] (*f'*) Golden.[4] (*g'*) Lindsay and Knorp.[3]

Gross Anatomy: The waxy resilient properties of amyloid have long been noted, and the gross appearance of the liver and the spleen involved in secondary amyloidosis is well known. When these properties are found associated with mesenteric fat and abdominal blood vessels, the appearance and the consistency are so unique that the diagnosis of primary systemic amyloidosis may be assumed. The appendices epiploicae, having been transformed into amyloid, lose their normal yellow color and soft consistency and become rigid, grayish and opalescent (fig. 4). Other abdominal fat, if changed, is similar. The small arteries and veins are conspicuous because of their uniform thickening and unusual cartilaginous consistency. They do not collapse when severed, and a clicking noise may be elicited by tapping the edge of a vessel with the knife or the finger nail. It is our opinion that when the deposits of amyloid are extensive enough to produce these changes, iodine and sulfuric acid may be relied on to confirm the diagnosis based on the gross specimen.

Staining Properties of Amyloid: Special stains were employed extensively in the microscopic study in both cases with the following results:

1. Masson's trichrome stain; Mallory's aniline–methylene blue stain: Amyloid and collagen are similar in these preparations. These stains, therefore, are not specific but are helpful in showing the gradation between amyloid and normal muscle in such tissues as the heart and the gastrointestinal tract.

2. Crystal violet: Both frozen sections and paraffin blocks were used. Mounts were not permanent, and contrast was not reliable. Cytologic detail was not clear.

3. Congo red: This stain as used by us was not as specific as crystal violet, and proper decolorization was difficult. However, decolorization, if thorough, resulted in a dependable positive amyloid stain. Furthermore, it afforded more permanent mounts and offered cellular detail as clear as that of hematoxylin and eosin preparations.

4. Phosphotungstic acid–hematoxylin: Amyloid stained reddish orange, in sharp contrast to the blue or dark red of surrounding tissue. This stain is excellent for low power work or for kodachrome preparations.

5. Verhoeff–Van Gieson elastic tissue stain: Amyloid stained green-beige and was therefore easily distinguished from hyaline and collagenous fibers. This stain was also useful in showing the changes in the reticular pattern in underlying structures (fig. 9).

With the aforementioned stains, the color in some areas otherwise morphologically identical was not always uniform. In this respect the amyloid change is similar to other protein alterations, such as fibrinoid

necrosis. This variation is explained by some workers as indicating a preamyloid stage of the formation of the final product.[13] It is not improbable that there are several or many different types of protein identified as amyloid, just as there are several types of Bence Jones protein and hyalin. In general, the microscopic identification of amyloid was inescapable if the unknown substance resembled amyloid in hematoxylin and eosin stain and if it was stained red in a well decolorized congo red preparation, orange by phosphotungstic acid–hematoxylin and green-beige by the Verhoeff–Van Gieson elastic tissue stain.

Ladewig's method of polariscopic examination of formaldehyde-fixed materials stained with congo red was employed.[14] Results varied considerably. Definite birefringence was noted only in the vessels of the tongue and the kidney in case 1.

Numerous other stains were used, but they contributed little to the understanding of the specific properties of amyloid and the manner in which the deposit of amyloid is related to the surrounding tissue.

Microscopic Anatomy.—Alteration of Fat: As noted in a foregoing paragraph, changes in fat are not unusual. They may be distinguished grossly, but more often are discovered only in microscopic sections. Wild [12a] reported the first case of primary systemic amyloidosis in 1886 and mentioned alteration of fat. Beneke, Pick, Lubarsch and Strauss further emphasized the frequency of involvement of mesenteric fat and epicardium.[15] Gerstel [12n] in 1932 described alterations of fatty tissue which were observed throughout the body, and Lindsay and Knorp [8] in 1945 reported that fatty bone marrow had been converted into amyloid.

Case 1 showed extensive alteration of fat both grossly and microscopically. Our interpretation of many sections suggests that the earliest change may be a mere accentuation of the cell membrane of each fat cell in a certain area. Adjacent capillaries are not necessarily involved. The thin pink ribbon of amyloid outlining the cell becomes thicker, fusing with that of adjacent fat cells, until gradually the entire section may be converted into a mass of amyloid of a honeycomb structure, broken only by the large globules of neutral fat (fig. 8).

It seems, therefore, that the change is not actually in the fat itself but in the protein substance of the membrane of the fat cell. This finding seems to corroborate the view of Peters [16] that the amyloid is deposited primarily in or on the cell rather than in the interstices of connective tissue.

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13. Eklund, C.: Bull. Staff Univ. Minnesota Hosp. **5**:180, 1934.
14. Ladewig, P.: Nature, London **156**:81, 1945.
15. Lubarsch.[1] Beneke.[12e] Strauss.[12p] Michelson and Lynch.[12r]
16. Peters, J. T.: Arch. Path. **35**:832, 1943.

Bone Formation: Calcification of vessel walls has been described by Götze and Krucke [12a] in a case of amyloidosis. Koletsky and Stecher [2] in 1939 mentioned cartilage and bone formed in the endocardium in their case of primary systemic amyloidosis, and Warren in 1939 described bone formation associated with amyloid deposited in the breast.

Bone formation occurred at the periphery of a mass of amyloid in the mesenteric fat in case 1 (fig. 10). This is of interest because of the prominence of reticuloendothelial cells in this region and the speculation it arouses as to the protein nature of amyloid itself.

Amyloid Casts: Anatomic changes of the kidney have been mentioned in preceding paragraphs of this comment. Slight contraction of the kidneys was observed in both cases. It was due to hyaline alteration of arterioles in case 2 and to amyloid changes of arteries and arterioles in case 1. In the latter there was also diffuse hyaline and amyloid alteration of glomeruli at the extreme periphery of the renal cortex. In addition, waxy, almost laminated casts were seen in some of the renal tubules (fig. 11). Waxy casts have been observed in the urine of patients with amyloid nephrosis, but no similar casts have been previously demonstrated in microscopic sections. These casts were few and distinguishable from ordinary albuminous and hyaline casts not only by their apparently increased density but also by the dark nuclei which clustered at their periphery, forming giant cells. These casts were so similar to those seen in Bence Jones proteinuria that additional sections were stained simultaneously with sections from kidneys obtained in 4 cases of multiple myeloma. The casts of Bence Jones protein failed to retain the congo red, and after strong decolorization the amyloid casts (case 1) remained positively stained.

Intracellular Amyloid: The question of intracellular amyloid is of fundamental importance to the understanding of the mechanism of the formation of this peculiar substance.

As early as 1885 Rokitansky [17] defined amyloid as an abnormal substance of the blood infiltrating cells of the reticuloendothelial system. Krawkow [18] in 1895 produced amyloidosis experimentally in rabbits and described giant cells which contained amyloid. He was of the impression that the amyloid was taken up and broken down by these cells. Giant cells containing amyloid, also observed in experimental amyloidosis, were described by Bailey [19] in 1916. Grayzell, Jacobi, Maslow and Warshall [20] produced amyloid in white mice by injecting a 5 per cent sodium caseinate solution subcutaneously. They observed amyloid within cells of the reticuloendothelial system. Grayzell and

17. Rokitansky, cited by Pearlman.[28]

18. Krawkow, N. P.: Centralbl. f. allg. Path. u. path. Anat. **6**:337, 1895.

19. Bailey, C. H.: J. Exper. Med. **23**:773, 1916.

20. Grayzell, H. G.; Jacobi, M.; Maslow, H., and Warshall, H. B.: Proc. Soc. Exper. Biol. & Med. **28**:172, 1930.

Jacobi [21] attributed this finding to the functioning of the reticuloendothelial cells in endogenous protein metabolism. Over a long period the phagocytic cells are unable to take care of increasingly large amounts of certain kinds of split protein (amyloid); eventually they fuse as giant cells, disintegrate and, together with the amyloid, form extracellular deposits.

Dick and Leiter [22] injected various bacteria into rabbits and produced amyloidosis. They attributed the presence of reticuloendothelial cells to a resorptive function. The amyloid, losing its staining properties, broke up into fragments and gradually disappeared. Foreign body giant cells participated in this process in 3 animals.

In case 1 reticuloendothelial cells containing droplets of congo red–stained material were seen in sections of mesenteric fat (fig. 12). These were in areas of chronic inflammation at the periphery of masses of amyloid. These cells were so few and the accumulations of amyloid so massive that it is easier to conceive of their function as being one of phagocytosis of amyloid than one of formation of amyloid.

Cells other than those of the reticuloendothelial system are known to contain amyloid. Schmidt [23] referred to epithelial cells of the liver and the kidney as containing droplets of amyloid and concluded that the material had been imbibed by dying cells.

Silwer and Lindblom [12g] described an alteration of myocardial fibers resembling intracellular amyloid. Larsen [12l] in 1930, finding similar changes, made serial sections and explained the intracellular amyloid as having invaded the fiber from without.

In cases 1 and 2 definite alteration of portions of skeletal muscle without apparent invasion of sarcolemma was seen. Myocardium and smooth muscle showed similar changes. A faintly positive amyloid stain was first seen in muscle fibrils which had become swollen and curled. Other fibrils, more severely affected by granular changes, stained more definitely. A more advanced change was similar to that seen in Zenker's degeneration, with the exception that the dark nodular swellings stained positively for amyloid. Eventually entire bundles were unmistakably converted to amyloid.

These changes which occurred at a distance from altered interstitial tissue or blood vessels seem to suggest definitely that amyloid may form intracellularly. They do not indicate, however, that amyloid may not form primarily in other sites. This has been clearly demonstrated by Krawkow,[18] who found the earliest change in experimental animals in the adventitia of blood vessels, and more recently, by Stemmerman and Auerbach [24] in a review of 468 cases of secondary amyloidosis.

21. Grayzell, H. G., and Jacobi, M.: Ann. Int. Med. **12**:39, 1938.
22. Dick, G. F., and Leiter, L.: Am. J. Path. **17**:741, 1941.
23. Schmidt, M. B.: Verhandl. d. deutsch. path. Gesellsch. **7**:2, 1904.
24. Stemmerman, M. G., and Auerbach, O.: Arch. Int. Med. **74**:384, 1944.

Giant Cells: The presence of giant cells as a constant feature of cases 1 and 2 (figs. 6, 8, 11, 13 and 15) stimulated a review of the literature in an effort to ascertain whether giant cells are an integral part of the anatomic picture of amyloidosis.

Giant cells have long been noted in experimental amyloidosis. This is illustrated by the work of Krawkow,[18] Bailey,[19] Dick and Leiter[22] and by Grayzell and associates[20] cited in a foregoing paragraph of this comment.

It was of interest to us that the early German writers stemming from Virchow treated the presence of giant cells in tumor-forming amyloidosis almost casually. Schmidt[23] in 1904 mentioned giant cells as present in local amyloid tumors. This information was incorporated in the discussion of the subject in one well known German textbook of pathology.[25] Foreign body giant cells were described as occurring in amyloid tumors of the eyelids,[26] and Lubarsch and Borchardt[9] reported a case in which an amyloid deposit seen in the stomach was accompanied by giant cells.

Herxheimer and Reinhart[27] in 1913 reviewed cases of local deposition of amyloid and objected to the former dogmatic view that foreign body giant cells were characteristic only of tumor-forming amyloidosis. Although they cited 3 cases of secondary amyloidosis with giant cells, recent extensive reviews[28] of cases of this type of amyloidosis do not mention the presence of giant cells. However, the hesitancy shown by these German workers in accepting the traditional dogma is justified by a review of one typical series of cases of local deposition involving the urinary tract, in which 5 of 9 cases showed giant cell reaction[29] (table 2).

In the cases of primary systemic amyloidosis reviewed by us the presence of giant cells was by no means a rare phenomenon, as illustrated in the 7 cases summarized in table 3.

The exact origin of the giant cells appearing in amyloidosis has not been determined. The giant cells in Gruber's case of amyloid alteration

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25. Dietrich, A.: Allgemeine Pathologie und pathologische Anatomie, Leipzig, A. Hirzel, 1939, vol. 1, pp. 81-85.

26. Kümmell, R. L., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 11, pt. 2, p. 192.

27. Herxheimer, G., and Reinhart, A.: Berl. klin. Wchnschr. **50**:1648, 1913.

28. Pearlman, A. W.: Quart. Bull. Sea-View Hosp. **6**:295, 1941. Rosenblatt.[11] Stemmerman and Auerbach.[24]

29. (*a*) Tilp, A.: Centralbl. f. allg. Path. u. path. Anat. **20**:913, 1909. (*b*) von Albertini, A.: Frankfurt. Ztschr. f. Path. **33**:248, 1926. (*c*) Solomin, P.: Prag. med. Wchnschr. **22**:3, 1897. (*d*) Luksch: Verhandl. d. deutsch. path. Gesellsch. **7**: 34, 1904. (*e*) Chwalla, R.: Urol. & Cutan. Rev. **36**:381, 1932. (*f*) Corbitt, R. W.; Broders, A. C., and Pool, T.: J. Urol. **52**:153, 1944. (*g*) Lehmann, G.: Zentralbl. f. allg. Path. u. path. Anat. **68**:209, 1937. (*h*) Akimoto, K.: Beitr. z. path. Anat. u. z. allg. Path. **78**:239, 1927. Herxheimer and Reinhart.[27]

of gastric smooth muscle are very similar to those in our case 2 (fig. 15). Gruber [30] suggested that they represented either nuclei of muscle fibers clustered together to resemble giant cells or regenerating smooth muscle.

The fact that these giant cells resemble Aschoff cells and that they are frequently located at the periphery of vascular deposits indicates that they may originate from the adventitial cells of blood vessels. In some areas the giant cells are associated with tiny capillaries resembling endothelial buds.

TABLE 2.—*Giant Cells in Tumor-Forming Amyloidosis of the Urinary Tract*

Location	Author	Giant Cells
Urethra	Tilp [29a]	None
	Herxheimer and Reinhart [27]	None
	von Albertini [29b]	Multinucleated giant cells with nuclei centrally or peripherally placed
Bladder	Solomin [29c]	Foreign body giant cells
	Luksch [29d]	None
	Chwalla [29e]	None
	Corbitt, Broders and Pool [29f]	Foreign body giant cells
Ureter	Lehmann [29g]	Numerous foreign body giant cells in submucosa
Renal pelvis	Akimoto [29h]	None

TABLE 3.—*Giant Cells in Primary Systemic Amyloidosis*

Author	Year	Comment
Koller [12m]	1932	Endothelial proliferation of vessels resembling giant cells
Strauss [13p]	1933	Many giant cells, probably formed from endothelial and adventitial cells; important in resorption of amyloid. Giant cells in bladder, pericardium, aorta, cervical and inguinal lymph nodes, etc.
Reimann, Koucky and Eklund [6]	1935	Giant cells at the periphery of masses in the cervix, nuclei irregularly arranged; no inclusions
Ferris [12n]	1936	Cases 1 and 2. Giant cells in alveolar masses and in bronchi; cytoplasm poorly differentiated from adjacent amyloid
Koletsky and Stecher [2]	1939	Giant cells frequent at periphery of amyloid masses
Pearson, Rice and Dickens [12b']	1941	Giant cells in larynx, trachea, fat, skin, etc.

The most probable precursor, however, is the reticuloendothelial cell, whose primitive properties are well known. These cells not only are prominent in the tissues of experimental animals with amyloidosis but are frequently seen in human cases of primary systemic amyloidosis. Pulinger and Pirie [31] found that multinucleated giant cells closely fol-

30. Gruber, G. B., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1929, vol. 6, pt. 2, p. 203.

31. Pulinger, B. D., and Pirie, A.: J. Path. & Bact. **54**:341, 1942.

lowed the reticuloendothelial cells appearing at the site of cornea implanted in the rabbit. They explained this reaction, which developed within six weeks, on the basis of the presence of an insoluble protein. Such a conclusion seems further justified when one contemplates the viscous, waxy properties of amyloid and the giant cell reaction associated with the amyloid casts in case 1.

SUMMARY

Two cases of primary systemic amyloidosis are presented. They illustrate certain distinctive anatomic features which deserve emphasis: fat altered by deposition of amyloid, seen in the gross specimen as well as in the microscopic section; giant cells associated with amyloid deposits; intracellular amyloid; bone formed in the vicinity of amyloid; renal tubules containing amyloid casts, heretofore undescribed.

The significance of these features is discussed as it relates to the genesis of amyloidosis. Their conservative interpretation, however, permits no new conclusions as to the nature and origin of this peculiar protein.

Relative to the experimental observation of hyperglobulinemia [32] preceding the deposition of amyloid, it is of interest that high serum globulin was seen in case 2. There is no record, however, that serum globulin was high early in the history of the first patient, before the precipitates of amyloid became so extensive.

If plasma globulins do participate in the formation of amyloid, it is our opinion that the preexisting protein within, on or around the cell is also necessary to its formation. On any other basis it becomes difficult to explain how amyloid occurs not only in the location of interstitial fluid but also within collagen and muscle fibers, the membrane of the fat cell and the walls of veins and arteries. This finding lends itself to the theory of an antigen-antibody mechanism of the formation of amyloid [33] and allows for the varying distribution of this protein in the several types of amyloidosis.

Staining reactions indicate that the different forms of amyloid, like collagen, hyaline material and the several varieties of Bence Jones protein, are chemically related substances of varying viscosity, distribution and mechanism of formation.[34] The more viscous insoluble proteins may be accompanied by reticuloendothelial cell reaction and consequent giant cell formation.

The photographs were made by Mr. Carl M. Bishop.

32. Eklund, C. M., and Reimann, H. A.: Arch. Path. **21**:1, 1936.

33. Loeschke, H.: Beitr. z. path. Anat. u. z. allg. Path. **77**:231, 1927.,

34. Hueper, W. C.: Arch. Path. **39**:207, 1945. Bayne Jones, S., and Wright Wilson, D.: Bull. Johns Hopkins Hosp. **33**:119, 1922. Forbus, W. D.; Perlzweig, W. A.; Parfentjev, I. A., and Burwell, J. C.: ibid. **57**:47, 1935.

MECHANISMS CONCERNED IN THE NECROSIS EFFECTED BY UNSATURATED FATTY ACID

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THE ACTION of the sclerosing agent sodium morrhuate,[1] as is well known, is associated largely with its effect on the blood. Thrombosis of the renal artery follows an injection of 60 to 100 mg. of a saline solution when the circulation is only temporarily interrupted. Preliminary heparinization prevents thrombosis, even though the blood vessel walls are extensively damaged and the epithelium of the renal tubules is necrosed. As the quantity of this unsaturated compound is decreased, the injury to the vessel walls becomes negligible at a time when the necrotizing effect[2] on the renal tubular epithelium still is at its height. Similar results were secured with two well defined unsaturated fatty acids.

On the other hand, "saturated" morrhuate when injected into the renal artery produces no demonstrable damage either of the vessel walls or of the renal epithelium. This fact together with the observation that the unsaturated compound is harmless when injected into the uninterrupted general circulation led us to combine serum and also serum albumin with the morrhuate prior to injecting it into the renal artery. These experiments are detailed in the presentation that follows.

MATERIALS AND METHODS

Sodium morrhuate (5 per cent), adjusted to p_H 8.6 and diluted with saline solution, was used in many of the experiments. The "saturated" compound was prepared[3] by adding hydrochloric acid to the sodium salt and removing the free acid, which was then carefully dried on a steam bath and taken up in chloroform. After addition of bromine in methyl alcohol, three hours' protection from light, removal of the precipitate and evaporation of the supernatant fluid to dryness in an air stream, the residue was taken up with chloroform, the chloroform evaporated

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From the Laboratory of Pathology, Yale University School of Medicine.

1. Jensen, H., and Jannke, P.: J. Am. Pharm. A. **33**:362, 1944.

2. Ochsner, A., and Mahorner, H.: Arch. Surg. **29**:397, 1934. Scheman, L.; Lewin, P.; Sideman, S., and Janoba, M.: Am. J. Surg. **60**:371, 1943.

3. Trappe, W.: Biochem. Ztschr. **296**:180, 1938.

and the saturated acid converted into the soap with sodium hydroxide and water. Undissolved particles were removed, the dry weight of soap per cubic centimeter was determined and the hydrogen ion concentration was adjusted to p_H 8.6.

The sodium salt of "pure" linoleic acid was prepared by addition of alcoholic sodium hydroxide. This same procedure was followed with linolenic acid. The hydrogen ion concentrations of the two solutions were adjusted to p_H 8.6.

Dog serum albumin was prepared by saturation of serum to 55 per cent with ammonium sulfate, removal of the precipitate, dialysis of the supernatant fluid, lyophilization and resolution of the protein to a concentration of 1.6 per cent in saline solution.

Technic of Injection.—After removal of the right kidney (pentobarbital sodium anesthesia), the left renal artery was occluded deep in the wound with a rubber shod clamp, the ureter was similarly clamped, the kidney was freed of blood by gentle massage, and the vein was compressed with a third clamp. With a 25 gage hypodermic needle, bent to a convenient angle, about 80 degrees, the lumen of the renal artery was entered and the required amount of solution delivered. When the main artery was not accessible, it was necessary to divide the solution between branches, two or three arteriopunctures being made to insure even distribution. Four minutes after the injection the clamps were removed from ureter, vein and artery in this order. Bleeding from the site of the arteriopuncture was usually controlled by pressure, insufficient to occlude the artery, for a few minutes or by applying a fragment of muscle to the bleeding point. The kidney was then replaced with care to avoid torsion of the pedicle, and the wound was closed. The procedure required thirty to forty minutes.

RESULTS

Dogs 1 and 2 were given 250 and 100 mg. of sodium morrhuate, respectively. Both became anuric and died after three and three quarters and four and a half days. Both showed destruction of the intima of renal arteries and veins, complete thrombotic occlusion of these vessels and associated death of renal tissue.

The next 5 dogs were heparinized four to five minutes before the renal vessels were clamped and the morrhuate injected. In none of these animals was there any evidence of thrombosis, not even in dog 3, which received 50 mg. of morrhuate (7.1 mg. per kilogram), the largest amount administered in this series. But, even in the absence of thrombosis, the damage inflicted on the kidney of dog 3 was extensive, and the animal promptly became almost anuric. The few cubic centimeters of urine excreted daily was rich in albumin and in hyaline and granular casts, and the nonprotein nitrogen of the blood rose to 323 mg. per hundred cubic centimeters on the fourth day shortly before death. Glomerular necrosis and hemorrhage, as well as tubular epithelial necrosis, were striking, and the walls of many smaller renal arteries were both edematous and necrotic.

Less fulminant signs followed the injection of smaller quantities of morrhuate, 0.55 mg. per kilogram, in dogs 5 and 6. The urinary output, actually increased at first, continued within the normal range; its rich

content of albumin and of hyaline and granular casts together with a blood nonprotein nitrogen content of 70 to 130 mg. per hundred cubic centimeters, was ample evidence of renal dysfunction. At death, on the tenth day, no significant changes were encountered either grossly or histologically in the renal vessels. Widespread necrosis of the tubular epithelium with casts of cellular detritus, focally impregnated with calcium, and epithelial regeneration, however, were conspicuous.

Little is known of the composition of the morrhuate beside the fact that it is the sodium salt of a mixture of many unsaturated fatty acids derived from cod liver oil. Since it seemed probable that the necrotizing effect was related to unsaturated acids in this mixture, the action of two well defined unsaturated fatty acids, sodium linoleate and sodium linolenate, was studied. From 1.5 to 2.5 mg. per kilogram of one or the other of these compounds was injected into the renal arteries of 4 heparinized dogs. Numbers 12 and 14 died in acute uremia after four and six and a half days, respectively. Number 13 remained suburemic until death, at the end of the fourth week. Number 15, seriously sick for two weeks after the injections, with the blood nonprotein nitrogen as high as 186 mg. per hundred cubic centimeters, slowly recovered and survived.

The extensive tubular epithelial changes observed in the kidneys after the injection of the smaller amounts of morrhuate were also encountered in dogs 12, 13 and 14. On the other hand, some vascular involvement which the morrhuate-injured kidneys lacked was present in these 3 animals. They included obliteration of glomerular capillaries (dog 12), marked thickening of the walls with narrowing of the lumens of the arterioles, sclerosis of glomerular tufts (dog 13) and fibrinoid medial necrosis (dog 14).

These changes supported the view that unsaturated groups of the fatty acids are responsible for the extensive cellular damage. Three experiments were carried out to put the theory to a test. They involved substitution of the unsaturated morrhuate with the "saturated" or brominized homolog. From 1.7 to 2.2 mg. per kilogram was injected into the renal arteries of three dogs, 9, 10 and 11, but no discernible functional or structural damage was done to the kidney even when the injection was repeated two or three times at weekly intervals in the same animal. The urine remained normal in quantity and composition, and the blood nonprotein nitrogen showed only transient and insignificant elevation or none. Biopsies carried out at appropriate intervals revealed no damage of either tubules or glomeruli.

Contrasting with the results observed when the unsaturated fatty acids were injected into the renal artery under the conditions described was the absence of ill effects after much larger quantities of sodium morrhuate were injected into free-flowing nonheparinized blood. Dog

23 received 12, 27 and finally 70 mg. per kilogram in the vein of the leg on three successive occasions at weekly intervals without change of the preinjection normal blood pressure or blood nonprotein nitrogen content or of the volume or the constituents of the urine. When the kidney was studied five months later, scarring or other evidence of injury was lacking.

The enumerated findings led to still another procedure. The saline solution previously used to dilute the unsaturated acid was replaced with dog serum. When this combination was injected into the renal artery by the method outlined earlier, no functional or morphologic renal changes resulted. Neutralization by serum was prompt and quite as effective after two minutes as after one hour. Tested with 4 animals repeatedly, in several as many as four times, the quantity which had resulted in death with extensive renal change when a saline mixture was used, was found innocuous.

Dog serum albumin was found to be quite as satisfactory as the serum itself in eliminating the effect of unsaturated sodium morrhuate injected into the renal artery. Three cubic centimeters of a preparation containing 48 mg. of albumin was mixed with two or more times the fatal quantity of the saline solution–morrhuate combination. Such preparations were found to have no demonstrable functional or morphologic effects on either the animal or its kidney in three separate experiments.

SUMMARY

The thrombosis which develops when sodium morrhuate or the sodium salts of other unsaturated fatty acids are injected into the renal artery is prevented by preliminary heparinization, even though the quantities of these agents are adequate to effect extensive edema and necrosis of the blood vessel walls.

As the amount of the unsaturated acid is reduced, the greater sensitivity of the epithelium of the kidney as compared with the renal vessel walls becomes apparent. Extensive epithelial necrosis, with slight glomerular or other vascular change, follows.

The sodium salt of the saturated fatty acid injected into the renal artery under similar conditions and at the same p_H is harmless.

The unsaturated acid may be injected into the general circulation without ill effects. This is apparently the result of a neutralizing action of serum albumin, as was shown when a mixture of dog serum and unsaturated sodium morrhuate and a mixture of dog serum albumin and this compound were injected into the renal artery. Under these circumstances the functional and structural effects of the unsaturated compounds are eliminated.

Technical assisatnce was given by Mr. Edward Iannucci.

MYOCARDIUM AFTER SULFONAMIDE THERAPY

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ALTHOUGH the sulfonamide drugs have been replaced in many situations by the antibiotic agents, the indications for their administration are still many, and interest in their side effects, as well as in their therapeutic effects, should continue.

This study was undertaken in an attempt to determine whether or not any fairly constant pathologic changes observed in the myocardium could be reasonably attributed to the use of the sulfonamide drugs. French and Weller[1] have reported that interstitial myocarditis occurred in 55.5 per cent of 227 cases in which the patient had taken one of the sulfonamide drugs before death and in which other known causes of interstitial myocarditis had been excluded. The myocardial lesion which they reported finding consisted of collections of large mononuclear cells of the clasmatocytic type and, characteristically, numerous cells with granular eosinophilic cytoplasm. They found no constant significant changes in the interstitial supportive tissues or in the muscle fibers themselves. These workers found similar collections of cells, with many eosinophils, in 63.3 per cent of 60 mice and in 70.2 per cent of 47 rats that had received various sulfonamide preparations.

This work of French and Weller is the only recorded extensive study of sections of human hearts obtained at necropsy after treatment with the sulfonamide drugs. Although no other group has reported such a striking incidence of interstitial myocarditis following sulfonamide therapy, there have appeared reports,[2] for the most part of isolated

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The work was done in the section on pathologic anatomy of Mayo Clinic, under the supervision of Dr. A. H. Baggenstoss.

This article is an abridgment of a thesis submitted to the University of Minnesota Graduate School in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

1. French, A. J., and Weller, C. V.: Am. J. Path. **18**:109, 1942.

2. (*a*) Duff, G. L., and Murray, E. G. D.: Am. J. M. Sc. **205**:439, 1943. (*b*) Lederer, M., and Rosenblatt, P.: J. A. M. A. **119**:8, 1942. (*c*) Thompson, R. T., and Zeek, P.: Ohio State M. J. **41**:824, 1945. (*d*) Gessler, C. N.: South. M. J. **37**:365, 1944. (*e*) Wells, A. H.: Minnesota Med. **27**:1014, 1944. (*f*) Rich, A. R.: Bull. Johns Hopkins Hosp. **71**:375, 1942. (*g*) Schattenberg, H. J., and Harris, W. H., Jr.: J. Lab. & Clin. Med. **28**:671, 1943.

cases, in which it is stated that after the patient had taken a sulfonamide drug with or without signs of toxicity or sensitivity, microscopic section of the heart muscle obtained at necropsy revealed an excess number of interstitial cells; in some instances a predominance of eosinophilic cells has been described. Rich [2f] has observed such a lesion in association with lesions of periarteritis nodosa; others [2b, d] have observed miliary areas of necrosis together with the cellular collections. The presumption has been that the interstitial myocarditis has resulted from the administration of the sulfonamide drugs, as a manifestation either of toxicity or of hypersensitivity.

That certain persons are hypersensitive to the sulfonamide group of drugs is a recognized fact. That cellular collections may appear in the myocardium in man as the result of an individual patient's hypersensitivity to various agents seems quite probable.[3] Thus the stage would seem to be set for the appearance of cellular collections in the myocardium of some of the patients manifesting sensitivity to the sulfonamide series of drugs.

On the opposite side of the ledger one finds the reports of numerous workers who have carried out studies of the toxicity of various sulfonamide compounds with animals, in which no such lesions were detected in the microscopic sections of the heart.[4] In many of these studies the dose used was many times that used therapeutically in man. Merkel and Crawford [5] in a careful pathologic study of each of 5 patients whose deaths were attributed to sulfonamide drugs found no evidence of involvement of the heart. The very paucity of reports of interstitial myocarditis occurring in cases in which patients died as the result of sulfonamide intoxication, in spite of the rather high incidence of this intoxication reported in the literature, suggests the relative infrequency of this complication if it occurs at all.

One has but to scan the voluminous literature on myocarditis to realize how cautious one must be in attributing any given myocardial lesion to any specific therapeutic agent. Saphir,[6] in his extensive

3. Brown, C. E., and McNamara, D. H.: Arch. Dermat. & Syph. **42**:312, 1940. Clark, E.: J. A. M. A. **110**:1098, 1938. Clark, E., and Kaplan, B. I.: Arch. Path. **24**:458, 1937. Rich, A. R.: Bull. Johns Hopkins Hosp. **71**:123, 1942. Chafee, F. H.; Ross, J. R., and Gunn, E. M.: Ann. Int. Med. **17**:45, 1942.

4. Molitor, H., and Robinson, H.: J. Pharmacol. & Exper. Therap. **65**:405, 1939. Antopol, W., and Robinson, H.: Arch. Path. **29**:67, 1940. Davis, H. A.; Harris, L. C., and Schmeisser, H. C.: J. Lab. & Clin. Med. **25**:1263, 1940. Marshall, E. K., Jr.; Cutting, W. C., and Emerson, K., Jr.: J. A. M. A. **110**:252, 1938. Kolmer, J. A.; Brown, H., and Rule, A. M.: J. Lab. & Clin. Med. **24**:164, 1938. Nelson, A. A.: Pub. Health Rep. **54**:106, 1939. Wright, C. I., and Lillie, R. D.: ibid. **58**:1242, 1943. Endicott, K. M.; Kornberg, A., and Daft, F. S.: ibid. **59**:49, 1944.

5. Merkel, W. C., and Crawford, R. C.: J. A. M. A. **119**:770, 1942.

6. Saphir, O.: Arch. Path. **32**:1000, 1941; **33**:88, 1942.

review of the literature, noted that myocarditis had been reported in association with nearly every one of the infectious diseases, as well as with many other pathologic states. To confuse the picture further, there is a type of interstitial myocarditis, known variously as Fiedler's myocarditis, isolated myocarditis and idiopathic myocarditis; in cases of this type no cause for the myocarditis is apparent. After the condition was first described by Fiedler in the latter part of the nineteenth century, Helwig and Wilhelmy [7] found reports of 52 cases in the literature up to 1938. More recently Marcuse [8] has reported 36 cases of nonspecific myocarditis in which no causal factors were determined. The fact that myocarditis occurs spontaneously with considerable frequency in at least one experimental animal [9] represents an additional obstacle to the interpretation of such a pathologic occurrence.

The present study was undertaken in an attempt to determine whether or not there was either an abnormal number of interstitial cells or a predominance of a particular type of cell in the myocardium of the patient who had received sulfonamide therapy prior to death. In the discussion of my own findings I shall at times, for the sake of brevity, use the term "interstitial myocarditis" when speaking of those cases in which an excess number of interstitial cells were present in the myocardium. It should be understood that the term as I shall use it has the restricted meaning of "an interstitial reaction of the myocardial connective tissue" and may not represent inflammation in the usual sense of the word. All of the sections examined in this study were stained with hematoxylin and eosin.

PRELIMINARY STUDY

The numbers of cases of interstitial myocarditis indexed as such in the necropsy files of the Mayo Clinic for two five year periods were compared. In the period of 1930 to 1935 (before the sulfonamide era) 6 cases were observed and recorded, while in the period of 1937 to 1942 (during which time the sulfonamide compounds were being used freely) again only 6 cases were filed as such. Furthermore, in the latter group of 6 cases there were only 2 in which the patients had received any sulfonamide drug during their stay at the clinic prior to death.

Examination of the gross specimens of 50 hearts taken from the 1935 necropsy files (presulfonamide era), as controls, and of 40 hearts of persons who had received sulfonamide therapy prior to death revealed no gross changes which could be attributed to the sulfonamide drugs.

A study of the microscopic sections from 40 hearts selected at random from the 1935 necropsy files was undertaken in order to establish some conception of what constitutes "normal variations" in the muscle fiber, in the interstitial connective tissue and in the number and the types of interstitial cells. This was

7. Helwig, F. C., and Wilhelmy, E. W.: Ann. Int. Med. **13**:107, 1939.
8. Marcuse, P. M.: Arch. Path. **43**:602, 1947.
9. Miller, C. P., Jr.: J. Exper. Med. **40**:543, 1924.

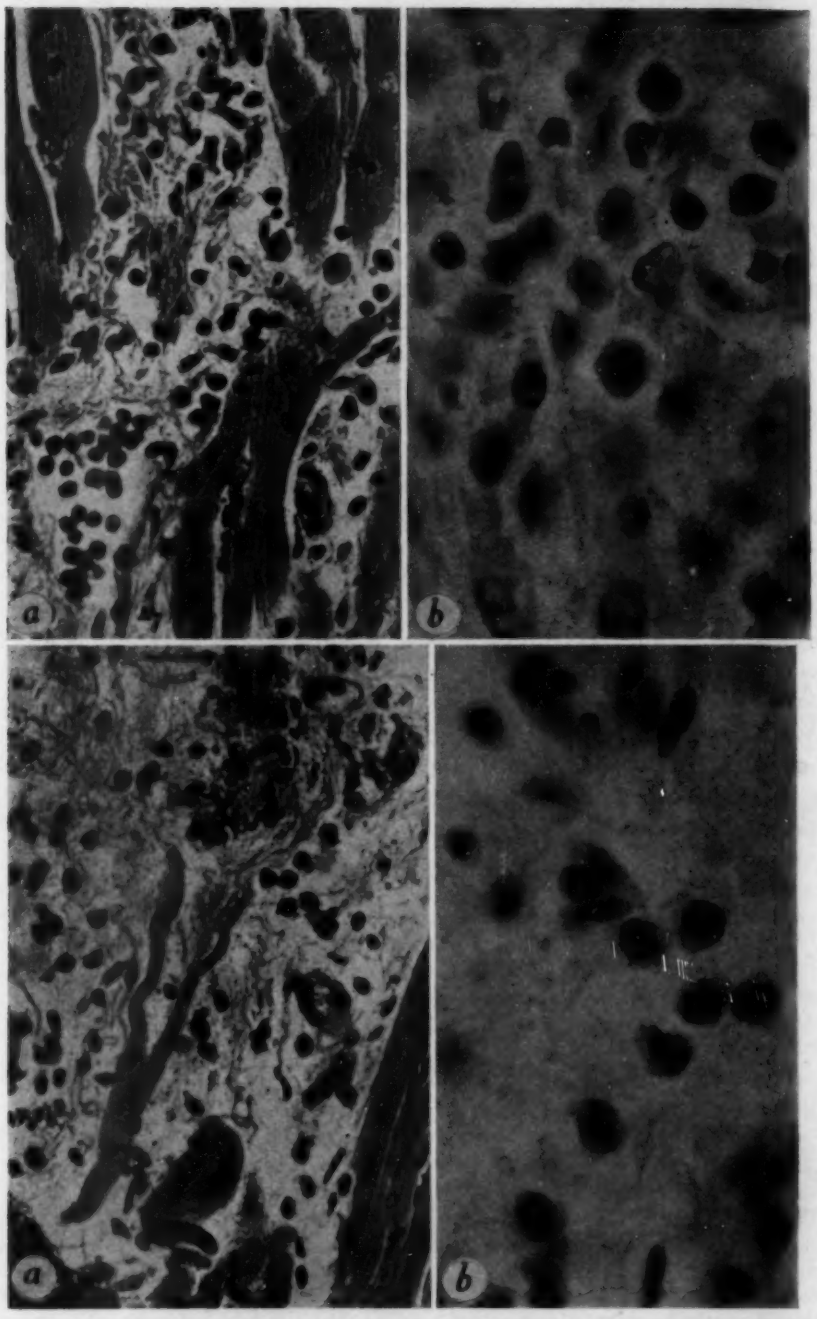

Fig. 1.—Upper: (*a*) Large and small mononuclear cells and lymphocytes (hematoxylin and eosin; × 400). The patient had received 12.5 Gm. of a sulfonamide drug before death. (*b*) Higher magnification showing cellular detail (× 1,000).

Lower: (*a*) Mononuclear cells, lymphocytes and a few myocardial reticulocytes (hematoxylin and eosin; × 400). The patient had received no sulfonamide drug before death. (*b*) Higher magnification showing cellular detail (× 1,000).

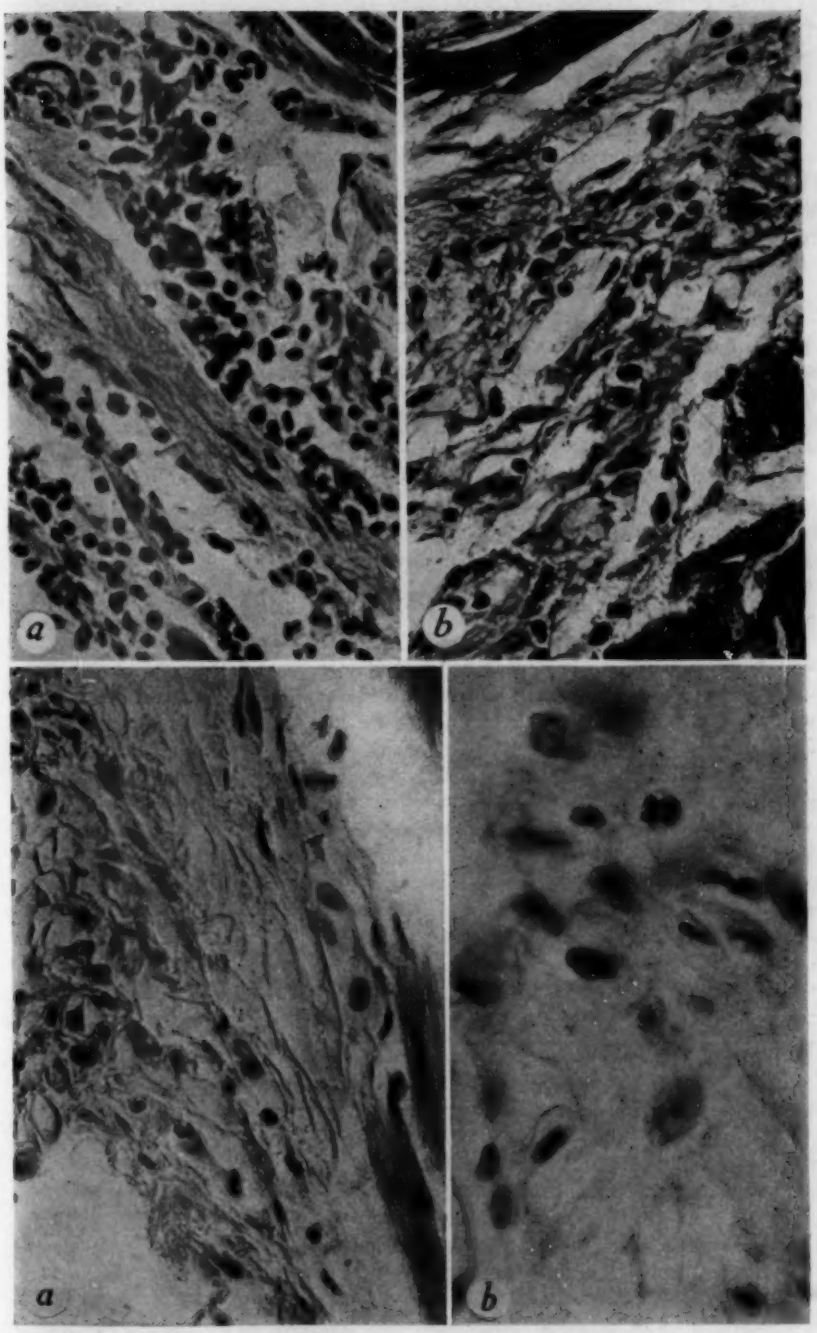

Fig. 2.—Upper: (*a*) Mononuclear cells and lymphocytes (hematoxylin and eosin; × 400). No sulfonamide drug was given. (*b*) Mononuclear cells, lymphocytes and a few myocardial reticulocytes (hematoxylin and eosin; × 400). Patient had received 37 Gm. of a sulfonamide drug before death.

Lower: (*a*) Myocardial reticulocytes (hematoxylin and eosin; × 400). No sulfonamide drug had been given. (*b*) Higher magnification to show myocardial reticulocytes (× 1,000).

followed by microscopic examination of the myocardiums of 30 patients to whom really large amounts of sulfonamide compounds had been administered before death.

Although tremendous variations were observed in the muscle fibers (degree of nuclear degeneration, loss of striation, fragmentation and other details) and in the interstitial tissue in individual cases, no significant or constant differences could be detected between sections representing the control group and sections representing the group which had received sulfonamide drugs.

The difficulty of saying what constituted the so-called normal number of interstitial cells and what represented an excessive number was apparent from the beginning. Polymorphonuclear neutrophils, lymphocytes, large and small mononuclear cells, myocardial reticulocytes and an occasional plasma cell and eosinophil were found in most of the sections examined. The large mononuclear cells (fig. 1; fig. 2, upper *a* and *b*) had a round, oval or indented nucleus which took the basic stain; the cytoplasm was usually slate gray. Many of these cells appeared to be of the clasmatocytic (resting-wandering cell) type. The cytoplasm of some of the mononuclear cells had an eosinophilic tinge; this was more apparent in the small than in the large mononuclear cells. I was unable to find mononuclear cells with eosinophilic granules or an excess number of eosinophils in the sections representing cases in which sulfonamide drugs had been given. The plasma cells exhibited the characteristic eccentrically placed nucleus, the "spokes of a wheel" arrangement of the nuclear chromatin and a slate gray to light blue cytoplasm. The myocardial reticulocyte, (fig. 1, lower *a* and *b*; fig. 2 upper *b* and lower *a* and *b*), first described by Anitschkow,[10] which is found exclusively in the heart, is thought to arise from the reticuloendothelial system. This rather unusual cell has, on longitudinal section, a spirochete-shaped nucleus.

No marked differences were noted between the two groups, but it was impossible to say from this preliminary study whether there was either an excess total number of interstitial cells or a predominance of any one type of cell in cases in the sulfonamide group. It was felt that an answer to the last two questions could be obtained only by a careful quantitative study of the numbers and the types of cells occurring in the myocardium. It was with this in mind that the principal study was undertaken.

PRINCIPAL STUDY

One hundred cases in which the patients were known to have received at least one of the sulfonamide drugs prior to death were studied. These cases were taken from the necropsy files at random except that in this group were included 30 cases in which the patients were known to have had massive doses of the drug and 2 cases in which the patients were known to have had a reaction to a sulfonamide drug as well as interstitial myocarditis. In this way it was felt that should a lesion be due to the sulfonamide compounds administered, it would be found in a significant proportion of this series.

One hundred cases taken from the 1935 necropsy files (presulfonamide era) served as controls. These cases were taken at random except for 12 cases of meningitis, 21 cases of pneumonia, 24 cases of peritonitis and 9 cases of septicemia. This selection was made in order that the control group might more nearly parallel the sulfonamide group, which, because of the very nature of the drug, was made up largely of cases of marked sepsis.

Cases were excluded from both groups if other lesions known to be associated commonly with myocarditis were present. Thus, cases of rheumatic fever,

10. Anitschkow, N. H., cited by Clawson, B. J.: Arch. Path. **32**:760, 1941.

diphtheria, syphilis, bacterial endocarditis, pyemia with myocardial abscesses and myocardial infarction, as well as all cases in which the coronary sclerosis was considered to be more than grade 2 (graded on the basis of 1 to 4 in which 1 represents the mildest and 4 the most severe condition), were thrown out.

As it seemed that a completely objective study could be made only by quantitative determination of numbers and types of cells, an arbitrary scale was set up for grading varying degrees of increase in the number of any individual type of cell (table 1), as well as a standard for grading the total increase of all cells in any given section (table 2).

Thus, when in any case the section of the myocardium had been studied and the cells of each type counted and the increase graded (by using table 1), the total increase of cells in the case could then be graded (by using table 2). For

TABLE 1.—*Standard for Grading the Increase of Each Type of Cell Found*

Type	"Normal" Limits of Count	Grade of Increase			
		1	2	3	4
Polymorphonuclear neutrophil	0-20	21-50	51-150	151-300	Above 300
Eosinophil	0-2	3-5	6-15	16-30	Above 30
Lymphocyte	0-20	21-50	51-150	151-300	Above 300
Large mononuclear	0-10	11-20	20-40	41-80	Above 80
Small mononuclear	0-5	6-10	11-20	21-40	Above 40
Plasma cell	0-5	6-10	11-20	21-40	Above 40
Reticulocyte	0-15	16-30	30-80	81-160	Above 160

TABLE 2.—*Standard for Grading the Total Increase of All Cells on the Section*

Grade	
1	Two or more types graded 1 One graded 1 and one graded 2 One graded 2 or one graded 3 alone
2	Two or more types graded 2 One or more graded 1 and one graded 3
3	Two or more types graded 3 One graded 2 and one graded 4
4	Two or more types graded 4

example, if the increase of lymphocytes was graded 1 and the increase of large mononuclears was graded 2, but no increase was noted in the other types of cells, that case would be credited with a grade 1 "total increase" of cells. It was felt that in any case of significant interstitial myocarditis the total increase would fall into grade 2, 3 or 4, while small degrees of increase of cells, which might be missed in other than a quantitative study, would fall into the grade 1 group.

Each section was studied under high power (× 430), the individual cells of each type were counted and the numbers recorded. As no two sections were exactly the same size and as the counting could not always be completely accurate, this was of necessity a rough quantitative study; this, however, applied equally to the sulfonamide and the control group. One hundred and forty-eight microscopic sections representing the 100 cases in which a sulfonamide drug had been given and 105 sections representing the 100 control cases were examined. The section from the septum of the heart was used in the quantitative study in the

great majority of cases, although sections of the right and the left ventricle and of the left auricle were studied; especial attention was paid those of the left auricle in view of the observations of French and Weller that many more cellular collections were seen in the less tightly packed auricular musculature.

Clinical data obtained from the necropsy protocol and case history included the age and the sex of the patient, the clinical diagnosis, the general anatomic diagnosis at death, the anatomic diagnosis of the condition of the heart, the type of sulfonamide compound given, the total dose, the duration of treatment, the interval between the end of treatment and death, the highest recorded blood concentration of the sulfonamide drug, the clinical manifestations of toxicity or

TABLE 3.—*Comparison of the Two Groups with Respect to Increase of Each Type of Cell*

Type	Cases in Which Count Was Within Normal Limits	Cases with Given Grade of Increase			
		1	2	3	4
Polymorphonuclear neutrophil					
Control group	81	15	3	1	0
Sulfonamide group	82	15	3	0	0
Lymphocyte					
Control group	62	27	11	0	0
Sulfonamide group	50	41	8	1	0
Large mononuclear cell					
Control group	88	9	3	0	0
Sulfonamide group	78	17	4	1	0
Small mononuclear cell					
Control group	71	21	6	2	0
Sulfonamide group	70	24	3	2	1
Plasma cell					
Control group	97	3	0	0	0
Sulfonamide group	94	4	2	0	0
Eosinophil					
Control group	100	0	0	0	0
Sulfonamide group	99	0	1	0	0
Reticulocyte					
Control group	76	21	3	0	0
Sulfonamide group	74	23	3	0	0

of drug sensitivity, the past history of either personal or family allergy and the past history of ingestion of sulfonamide drugs or of sensitivity.

RESULTS

In table 3 a comparative study of the sulfonamide and control groups with respect to the grading of increases of types of cells is presented. It can be seen readily that there is no significant difference in grading between the two groups for any of the types of cells studied and that no one type of cell predominates in the sulfonamide group. No significant difference could be found in the number of cells of any type in the auricular and the ventricular myocardium.

In table 4 the two groups are compared with respect to the total increase of all cells (table 2 being used as the standard for grading).

Thus it can be seen that in 35 per cent of the 100 cases of the control group the total increase of cells was graded 1 and in 3 per cent it was graded 2. In no cases of the control group was a grade 3 or 4 total increase noted.

In 2 additional cases, initially studied with the sulfonamide group, a grade 2 increase was noted (fig. 1, lower *a* and *b;* fig. 2, upper *a*). Subsequent analysis of the clinical data revealed that no sulfonamide drugs had been given. These 2 cases were not included in the control series inasmuch as the latter was limited strictly to material obtained from the 1935 necropsy files.

In the sulfonamide group of 100 cases a grade 1 increase was found in 31 per cent, a grade 2 increase in 5 per cent and a grade 3 increase in 1 per cent. In justice to the control group it should be mentioned that the single case in which there was a grade 3 increase in cells (fig. 1, upper *a* and *b*) and one of the cases (fig. 2, upper *b*) in which there was a grade 2 increase in the sulfonamide group were not taken at

TABLE 4.—*Comparison of the Two Groups with Respect to Increase of Total Collection of Cells*

	Cases in Which Count Was Within Normal Limits	Cases with Given Grade of Total Increase			
		1	2	3	4
Control group	62	35	3	0	0
Sulfonamide group	63	31	5	1	0

random but were specifically included in the study because in both of them sulfonamide sensitivity had been observed before death and interstitial myocarditis found after death. There were no other cases in which significant myocarditis (grade 2, 3 or 4 increase in cells) was associated with a history of sulfonamide toxicity or sensitivity.

Emphasizing further the absence of any significant increase of cellular collections in the sulfonamide group, subsequent analysis of the clinical data revealed that in 13 (65 per cent) of the 20 cases of the sulfonamide group in which the history suggested sulfonamide sensitivity or toxicity no increase in cells was noted; in 5 cases (25 per cent) a grade 1 increase, and in 1 case (5 per cent) a grade 2 increase (fig. 2, upper *b*) and in 1 case (5 per cent) a grade 3 increase (fig. 1, upper *a* and *b*), was noted. These figures are very similar to the figures recorded in table 4 for the control group and for the sulfonamide group as a whole, in spite of the specific inclusion of 2 cases of sensitivity associated with interstitial myocarditis.

Additional analysis of the clinical data in relation to the pathologic observations revealed nothing of significance and will be omitted from this paper. It should be mentioned that the four sulfonamide prepa-

rations in most common use (sulfathiazole, sulfapyridine, sulfanilamide and sulfadiazine) were all represented individually and in various combinations in the 100 cases studied.

SUPPLEMENTARY STUDY

While the present study was primarily one made of the human myocardium after sulfonamide therapy, the desirability of experimental studies to substantiate work in which so many variables were present was obvious. Although there was not sufficient time to carry out a detailed study with animals, I did have the opportunity, through the courtesy of Dr. H. E. Essex, of examining sections of the myocardiums of 9 white rats which had been given sulfonamide compounds orally in amounts calculated to produce in the blood concentrations of from 10 to 20 mg. per 100 cc. Nine white rats which had not been given sulfonamide compounds were used as controls. I examined these sections (using tables 1 and 2 in the grading) without knowing which were from the sulfonamide group and which were from the control group.

The results of this study were entirely negative: There was no significant increase in interstitial cells in the myocardium of any of these animals.

SUMMARY

An attempt has been made to determine whether interstitial myocarditis occurs in a significant proportion of cases in which patients have received sulfonamide therapy prior to death.

A comparison of the numbers of cases indexed as interstitial myocarditis in the necropsy files of the Mayo Clinic for two five year periods, prior to and following the advent of sulfonamide therapy, revealed exactly the same number of cases in each group.

A preliminary study showed in the myocardium neither gross evidence of change due to the sulfonamide drugs nor microscopic evidence of any change of the muscle fiber or of the interstitial supportive tissue for which these drugs could be blamed.

The principal study was a quantitative analysis of the types and of the total collections of interstitial cells in 100 cases in which sulfonamide drugs had been given and in 100 control cases (from the presulfonamide era). Cases were excluded from the study whenever other lesions were present which were known to be capable of producing myocarditis. Clinical data were obtained and analyzed in each case in the series.

In 35 per cent of the control group a grade 1 increase was noted in total collections of cells, while in only 31 per cent of the cases in the sulfonamide group was a similar degree of increase observed in the cells in the myocardium. In 6 per cent of the cases in the sulfonamide group

significant myocarditis (total cell increases) graded 2 and 3 was observed, compared with 3 per cent in the control group.

No one type of cell predominated in the sulfonamide group, nor were large collections of either eosinophils or mononuclear cells with eosinophilic granules observed. No differences were noted in the numbers or the types of cells between the ventricular and the auricular myocardium.

No significant correlation was detected between the type of sulfonamide given, the total dose, the duration of treatment, the interval between the end of treatment and death or the history of sulfonamide reactions and the histologic appearance of the myocardium.

The results of the study of animals, though grossly inadequate in number, did serve to corroborate those of the principal study; myocarditis was not noted in either the sulfonamide-treated rats or the controls.

For many years it has been a well known fact that evidence of interstitial myocarditis for which the cause is not apparent is found incidentally on microscopic examination of the heart. The possibility that the sulfonamide drugs may be responsible for the production of such a lesion in an occasional instance cannot be denied. In fact, work done elsewhere suggests that the production of such a lesion as a manifestion of sulfonamide hypersensitivity is a logical sequence of events. Two cases with such a combination of events were included in this study.

CONCLUSION

The results of the present study would indicate that the administration of sulfonamide compounds prior to a patient's death is not associated with either an increased total number of interstitial cells or an excess number of a particular type of cell in the myocardium in a statistically significant number of cases.

CHRONIC CARBON DIOXIDE POISONING

Experimental Studies

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EMPLOYEES of wine cellars and cold storage plants using dry ice and crews of submarines may undergo prolonged exposure to an atmosphere containing sublethal concentrations of carbon dioxide. Although the clinical, physiologic and chemical effects of such exposures have been studied in animals, no data are available as to the anatomic reactions elicited in the internal organs. Because of the practical and scientific importance of this aspect, the following experiments were performed.

EXPERIMENTAL PROCEDURE

Sixteen rats, 16 guinea pigs, 5 rabbits and 3 dogs were exposed to mixtures of carbon dioxide and air, in which the carbon dioxide concentrations ranged from 1 to 26 per cent, while the oxygen pressure was kept normal. The animals inhaled this atmosphere for periods varying from five to six weeks and were killed at the end of these periods, after decompression, by decapitation. The gas mixtures were delivered through a gas meter into a glass-lined, air-tight cage. Gas analyses were made from time to time for controlling the composition of the mixtures used.

The tissues were fixed in 4 per cent formaldehyde solution, and in Carnoy's and Susa's mixtures as well as in absolute alcohol. Sections were prepared with hematoxylin-eosin, Van Gieson's stain, elastic tissue stain, Masson's trichrome stain, sudan III, Foot's silver impregnation and Kossa's calcium stain. Brain tissue was fixed in 96 per cent alcohol, embedded in celloidin (a concentrated preparation of pyroxylin) and, after sectioning, stained with toluidine blue.

HISTOLOGIC OBSERVATIONS

The development of organic lesions depended on the concentration of the carbon dioxide and on the duration of exposure. Thus, lesions were present in guinea pigs kept for forty-eight hours in an atmosphere containing 16 per cent carbon dioxide as well as in rabbits exposed for thirteen days to air with a carbon dioxide content of 4.5 per cent. Changes were present in the lungs of animals of all species. The hepatic and renal lesions were most marked in the rats. The examination of the brain has been limited so far to guinea pigs.

In the lung there were scattered groups of distended alveoli and alveolar ducts which showed swollen and homogeneous walls having the shape of sickles or bands.

From the Institute for Brain Research.

The homogeneous material stained red or orange with Masson's trichrome stain, contrasting vividly with the bluish-stained drops of edematous fluid occasionally adhering to the alveolar walls (fig. 1 *A*). The walls of the alveolar capillaries were

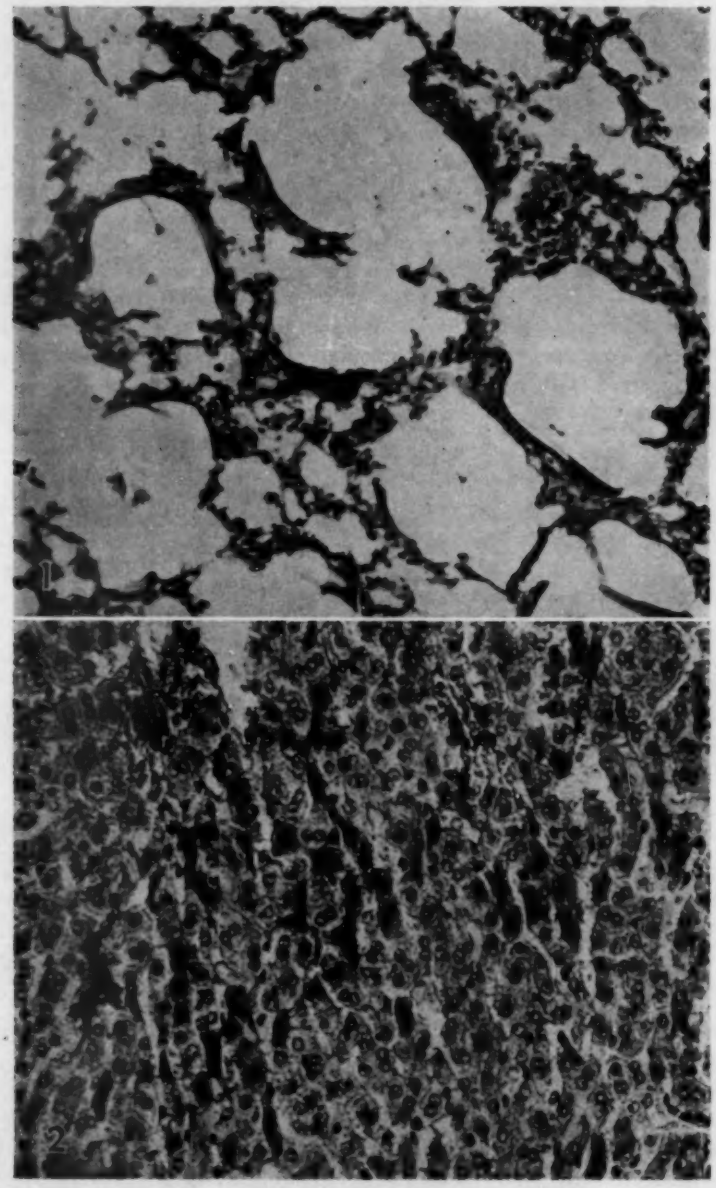

Fig. 1.—*A*, lung (guinea pig) with homogeneous fibrinoid bands in alveoli and alveolar ducts and edema. Masson trichrome stain; × 200.

B, liver (rabbit) with disseminate necroses in the periphery of a lobule and nuclear pyknosis. Hematoxylin-eosin; × 250.

included in the hyaline transformation and swelling. In hematoxylin-eosin preparations, blue-black colored bands were found within many alveolar ducts and in some respiratory bronchioles. These dark masses did not take the Kossa stain and contained in places coarse fragments of pyknotic cells. As a rule, some polymorphous leukocytes were present in the thickened walls beneath these deposits. The leukocytic infiltrations were marked in some parts of the lung and occasionally assumed the character of focal pneumonic lesions.

In the liver necrotic liver cells were scattered throughout the lobules. Between intact hepatic cells small groups of atrophic and pyknotic liver cells were found, which were surrounded by irregularly folded and swollen lattice fibrils (fig. 1 *B*), intensely blue colored, in sections stained with hematoxylin and eosin. The last-mentioned alterations were observed mainly in rabbits.

The lesions of the kidney were most clearly demonstrable in tissue fixed with 96 per cent alcohol or Carnoy's solution. The cellular lining of numerous tubules was completely necrotic and incrusted with lime, which often almost completely obstructed the tubular lumens in the form of casts. The tubules located in the cortical-medullary zone were affected most severely. The blue-black masses reacted positively with the Kossa stain. Acutely necrotic tubular epithelial cells

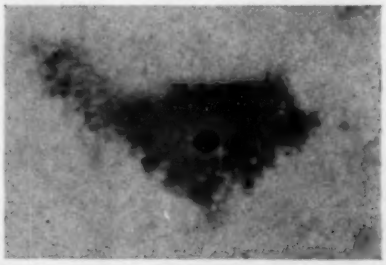

Fig. 2.—Ganglion cell of the nucleus angularis (Bechterew's nucleus) of the brain (guinea pig) showing enlarged nucleolus, shrunken nucleus and dissolved Nissl granules. Nissl stain; × 1,000.

showing loss of nuclear stain revealed beginning calcium incrustation. These lesions were particularly conspicuous in the kidneys of rats which had been exposed alternately and repeatedly to carbon dioxide–air mixtures and normal air. They were similar to lesions seen in mercury poisoning or hypochloremia.

The brain had irreversible degenerative changes in ganglion cells of various cerebral nuclei, of the basal ganglions, of the cerebral cortex and of the brain stem. Single ganglion cells were usually affected (fig. 2).

COMMENT

The pulmonary degenerative changes observed, which obviously were the result of the high carbon dioxide concentration of the inhaled air, occurred in several degrees of severity, revealing thereby their morphogenesis. After the cells lining the alveoli, alveolar ducts and respiratory bronchioles have become necrotic and their nuclei pyknotic, the chromatin masses sinter and form thereby the blue-black bands cover-

ing the inside of these conduits. The lesions of the swollen alveolar septums undergo fibrinoid necrosis. Fibrin from the damaged capillary walls mixes with the necrotic material in the walls and contributes to the final condition of a fibrinous inflammation. A massive leukocytic infiltration of these necrotic patches may give rise to pneumonic foci. Similar pulmonary reactions are elicited by experimental oxygen poisoning (Pichotka [1]), by poisoning with phosgene (Aschoff [2]) and by the related condition known as "pneumonosis" (Moell [3]).

The lesions occurring in the liver, the kidney and the brain of the animal exposed to toxic concentrations of carbon dioxide are simple necrotic reactions. In the kidney they are complicated by subsequent calcification, giving rise to a condition known as chalk nephrosis. The peculiar changes observed in the liver suggest that at least during the early stage they may be specific for carbon dioxide poisoning. The lesions of the liver, the kidney and the brain are not entirely due to the action of the increased carbon dioxide tension of the respiratory air, but represent in part the results of a "transmineralization" in which the loss of potassium, especially in the liver, apparently plays an important role. Further complications arise from the fact that when surviving animals are returned to normal atmospheric conditions, carbon dioxide is rapidly given off by the tissues, and a definite change of the ionic equilibrium of the blood and tissues ensues. This reaction may be important in connection with the calcification of already necrotic cells, which would be favored during the phase of alkalosis.

It must be emphasized that the organic lesions observed are not the result of anoxia, for throughout the experiments the oxygen pressure of the air inhaled was maintained at an almost normal level. In contrast to the anoxemic necrosis of the liver, affecting mainly the central portions of the organ, the hepatic degenerations seen in carbon dioxide poisoning involve mainly the periphery.

The observations made indicate that an excessive increase of the carbon dioxide tension of the inhaled air may cause severe degenerative and necrotic lesions of several internal organs. In assessing the required concentration of carbon dioxide, the difference of the lethal doses for different animals and species has to be taken into account, especially when one attempts to apply the findings to man. However, the present results suggest that it is not impossible for similar changes to develop in man under special conditions of exposure. The observations reported may have also a general biologic importance, though it is not yet

1. Pichotka, J.: Beitr. z. path. Anat. u. z. allg. Path. **105**:381, 1941.

2. Aschoff, L., in von Schjerning, O.: Handbuch der ärztlichen Erfahrungen im Weltkriege, Leipzig, J. A. Barth, 1914-1918.

3. Moell: Beitr. z. path. Anat. u. z. allg. Path. **105**:366, 1941.

possible to estimate the exact role which the end product of cellular respiration might play as a pathogenic agent in various diseases, especially in those interfering with the process of pulmonary respiration, such as silicosis.

SUMMARY

Dogs, rabbits, guinea pigs and rats exposed repeatedly and over long periods to sublethal doses of atmospheric carbon dioxide presented degenerative changes in the lungs, the liver, the kidney and the brain. These lesions were the result of the increased carbon dioxide tension and were not caused by anoxemia.

HEPATIC ABSCESS

Factors Determining Its Localization

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> And they talked about how Ohio water didn't like to mix with Mississippi water. Ed said if you take the Mississippi on a rise when the Ohio is low, you'll find a wide band of clear water all the way down the east side of the Mississippi for a hundred mile or more, and the minute you get out a quarter of a mile from shore and pass the line, it is all thick and yaller the rest of the way across.—*Mark Twain.*

IN 1901 SEREGE [1] reported that india ink injected into the superior mesenteric vein of the rabbit was carried to the right lobe of the liver whereas that injected into the splenic vein was carried to the left lobe. In a series of patients with dysenteric ulceration of the large bowel, he [2] found abscesses of the right lobe associated with lesions that were predominantly cecal, and abscesses of the left lobe associated with lesions that were predominantly rectal or sigmoidal. A similar distribution of hepatic involvement occurred with tumors metastasizing from these areas. He concluded that there were two relatively unmixed columns of blood flowing side by side in the portal vein, one from the superior mesenteric vein and one from the compound splenic and inferior mesenteric vein. The column from the superior mesenteric vein entered the right lobe of the liver; the one from the spleen and the inferior mesenteric area entered the left lobe. Subsequent investigations appear to have confirmed his conclusions. It is our purpose to review the subject briefly and to present a series of cases of abscess of the liver, contrasting the sites of origin of the abscesses that involved the right lobe and the sites of origin of those that involved the left lobe.

CLINICAL AND PATHOLOGIC MATERIAL

A series of reports of cases of abscess of the liver was collected from the autopsy files of the Beth Israel Hospital, the Mallory Institute of Pathology of the Boston City Hospital, the Massachusetts General Hospital and the Peter Bent

From the Departments of Pathology and Medicine of the Peter Bent Brigham Hospital and Harvard Medical School.

1. Serege, H.: J. de méd. de Bordeaux **31**:208 and 271, 1901.
2. Serege, H.: J. de méd. de Bordeaux **31**:291, 1901.

Brigham Hospital. The number of autopsies reviewed totaled 39,219. Two hundred and sixty-three cases of hepatic abscess were found. For 34 cases the records were incomplete, leaving 229 cases, which are analyzed in the following pages.

RESULTS

The results of a survey of the material are listed in three tables. Table 1 is made up from those cases in which there were multiple abscesses and in which both the right and the left side of the liver contained abscesses. Table 2 summarizes those cases in which there were single or multiple abscesses occurring in the right side of the liver alone, and table 3 lists the cases in which single or multiple abscesses

Abscess formation restricted to the left side of the liver of a 65 year old woman suffering from acute diverticulitis of the sigmoid.

occurred in the left lobe alone. There were 75 cases of abscesses of the right lobe, 18 cases of abscesses of the left lobe, and 136 cases of abscesses of both lobes.

The largest single group of cases of hepatic abscess was that in which infection followed obstruction of the common duct. This group was made up of 50 cases, or 22 per cent of the total number of cases studied. Septicemia accounted for the second largest group of cases. This group was made up of 25 cases with abscess formation in all lobes of the liver, 6 cases in which abscesses were found in the right side of the liver alone, and 1 case in which abscesses were present in the left lobe alone.

TABLE 1.—*Points of Origin of Abscesses Occurring in Both the Right and the Left Lobe of the Liver*

Source of Primary Infection	Cases
Obstruction of the common duct	50
Septicemia	25
Acute appendicitis with pylephlebitis	24
Bacterial endocarditis	9
Portal thrombophlebitis	9
Extension from subdiaphragmatic abscess	4
Metastatic from inflammation of the gastrointestinal tract	4
Primary: no known source	3
Amebic abscess	3
Direct extension of an abdominal inflammation	2
Direct extension of a perinephric abscess	1
Direct extension of empyema	1
Echinococcus infection	1
	136

TABLE 2.—*Points of Origin of Abscesses Occurring in the Right Side of the Liver Only*

Source of Primary Infection	Cases
Acute appendicitis	16
Acute appendicitis and pylephlebitis	2
Primary: no known source	8
Inflammation of gallbladder	7
Inflammation and pylephlebitis of gallbladder	2
Direct extension of inflammation of gallbladder	3
Septicemia	6
Subdiaphragmatic abscess	6
Extension of empyema	4
Extension of peritoneal inflammation	4
Inflammation of terminal part of ileum	4
Inflammation of cecum	3
Perinephric abscess	3
Amebic abscess	3
Inflammation of duodenum	1
Inflammation of right portion of colon	1
Bacterial endocarditis	1
Echinococcus infection	1
	75

TABLE 3.—*Points of Origin of Abscesses Occurring in the Left Side of the Liver Only*

Source of Primary Infection	Cases
Direct extension of inflammation associated with neoplasm of stomach	6
Direct extension of inflammation associated with ulcer of stomach	2
Direct extension of abdominal inflammation	2
Diverticulitis of sigmoid	1
Ulcer of rectum	1
Abscess of descending colon	1
Fistulas of ascending, transverse and descending colon	1
Typhoid ulcer of ileum	1
Neoplastic obliteration of left hepatic duct	1
Septicemia	1
Inflammation of gallbladder	1
	18

Eleven cases are recorded as instances of abscess "primary" in the liver. That is, no other source of the infection could be found at autopsy, nor was there any history suggestive of another point of origin. In 8 of the 11 cases the infection was restricted to the right lobe, while in 3 cases abscesses were found in both the right and the left side of the liver. In the majority of instances of right-sided infection there was multiple abscess formation.

Abscess formation restricted to the left lobe of the liver was relatively uncommon. When it did occur it was usually due to infection extending directly from an ulcerated carcinoma or an ulcer of the stomach which had become adherent to the liver. Invariably, in these cases, it was possible to demonstrate an opening between the necrotic cavity of the hepatic abscess and the lumen of the stomach. In 2 additional cases the inflammatory process had extended into the left lobe of the liver from an infection of the lesser peritoneal cavity. These 10 cases accounted for over half of the instances of abscess of the left lobe.

The gallbladder and the manner in which it is related to the localization of hepatic abscess deserves special mention. There were 12 instances in which abscesses occurring in the right lobe only were associated with inflammation of the gallbladder. In 3 cases the hepatic lesion was thought to be due to direct extension of the inflammatory process. Seven cases probably represented infection of the gallbladder metastasizing to the liver. This is to be expected, since in most persons the cystic vein empties directly into the right branch of the portal vein. In the remaining 2 cases there was associated pyelophlebitis of the right branch of the portal vein.

There were 24 cases in which abscesses formed in both the left and the right side of the liver, following acute appendicitis (table 1). In every instance there was associated pyelophlebitis. On the other hand, as can be seen from table 2, there were 18 cases of abscess forming in the right side of the liver only, following acute appendicitis, but in only 2 of these cases was there associated pyelophlebitis, and it was confined to the right portal vein. In other words, hepatic abscess following acute appendicitis tends to occur in the right lobe only unless there is associated portal pyelophlebitis, in which case the infection extends up the branches of the portal vein, with multiple lesions being formed throughout both sides of the liver.

Abscess of the right lobe alone was found in 27 patients in whom the primary focus of infection lay in the area drained by the superior mesenteric vein. Serege's rule appeared to hold. There was but one exception in the cases of solitary hepatic abscess, that in which a single abscess of the left lobe of the liver was associated with a typhoid ulcer

of the ileum. In 4 instances of primary infection of the area drained by the superior mesenteric vein, mixing of blood in the portal vein appeared adequate for the establishment of abscesses of both lobes, left as well as right. It is possible that seeding of infective material into the blood stream in these cases may have been particularly extensive or repetitive. It is also probable that persons vary in the degree to which the two columns of blood from the inferior and superior mesenteric veins mix within the portal vein. Be that as it may, no crossing over of infection from a focus in the inferior mesenteric area, with production of an abscess of the right lobe, was observed, perhaps because of the smallness of the number of cases studied and the relative infrequence of foci of infection in the inferior mesenteric area.

COMMENT

Though it is customary to speak of the liver as a single organ, there is reason for considering its right and left lobes, or more properly its right and left sides, independently. The two arise from separate outpouchings of the upper enteron [3] and, despite early fusion along a plane joining the fossa of the gallbladder and the point of exit of the hepatic vein, they retain considerable anatomic independence, particularly with regard to vasculature.[4] In addition to the internal autonomy of each lobe there is evidence that the streams of portal blood coming into the lobes are of somewhat different origins. In dogs the difference is readily demonstrated. Emulsified fat,[5] india ink [6] or radioactive phosphorus [7] injected into the superior mesenteric vein is carried to the right lobe; material injected into the inferior mesenteric or the splenic vein is carried to the left lobe. Similarly in man, it is recognized that processes metastasizing via the superior mesenteric vein tend to go to the right lobe, while processes coming from the areas of the inferior mesenteric, the gastric coronary or the splenic vein go to the left lobe.[8] The reason for the distinction appears to be that in the short common portal trunk the mixing of blood from the several branches is incomplete, with the result that columns of blood from the several abdominal areas may be directed toward different portions of the liver. The fact that portal

3. Prentiss, C. W., and Arey, L. D.: Embryology, Philadelphia, W. B. Saunders Company, 1921.

4. Cantlie, J.: J. Anat. & Physiol. **32**:iv-ix, 1897-1898. McIndoe, A. H., and Counseller, V. S.: Arch. Surg. **15**:598, 1927.

5. Bartlett, F. K.; Corper, H. J., and Long, E. R.: Am. J. Physiol. **35**:36, 1914.

6. Copher, G. H., and Dick, B. M.: Arch. Surg. **17**:408, 1928.

7. Hahn, P. F.; Donald, W. D., and Grier, R. C., Jr.: Am. J. Physiol. **143**: 105, 1945.

8. Karlmark, E.: Acta path. et microbiol. Scandinav., 1932, supp. 13.

blood flow is sluggish, begins and ends in venous capillaries and has, in consequence, a relatively low head of effective pressure lends evidence to the idea that turbulence and mixing within the portal vein may not be great.

The possibility that differences in portal blood supply affect the pathologic and the physiologic manifestations of the right versus the left lobe of the liver, aside from the localization of metastases, has received comment in a publication by Himsworth and Glynn.[9] In experiments concerned with protein deficiency, of a type for which methionine is protective, these observers found that in rats the cirrhotic process noted in cases of mild deficiency was confined to the left lobe of the liver. A similar tendency had been observed by Gillman[10] in his studies of the effect produced on the same animal by prolonged feeding of the staple diet of the African native. This diet, corn and sour milk, is notoriously associated with a high incidence of cirrhosis and carcinoma of the liver in the natives.[10] Finch, Hegsted and Kinney[11] found that in rats fed a diet of corn and lard for three weeks the liver cells of the left lobe contained large quantities of fat while those of the right lobe contained little or none.[11] The suggestion has been put forth[9] that since the portal blood comes to the right lobe predominantly from the small intestine, it may be richer in protective products of protein digestion than blood coming to the left lobe via the colon and the inferior mesenteric vein. Evidence that there may be a distinction between the nutritional environments of the two lobes in man, is not extensive, though some correlation may be drawn with the early experiments of Glenard[12] and Serege[13] and the exceptional degree of left lobe involvement at times observed in acute yellow atrophy of virus[14] or chemotoxic origin.[15] In any case it would be of interest if separate catheterizations of the hepatic veins were to reveal significant differences in the composition of blood emerging from the right and left lobes, respectively.

SUMMARY

A series of cases of abscess of the liver is presented, giving the location of the probable primary foci of infection.

9. Himsworth, H. P., and Glynn, L. E.: Lancet **1**:457, 1944.

10. Gillman, J.: Brit. M. J. **1**:149, 1944.

11. Finch, C. A.; Hegsted, D. M., and Kinney, T. D.: Unpublished data.

12. Glenard, F.: Lyon méd. **64**:5, 80, 115, 189 and 259, 1890.

13. Serege, H.: Compt. rend.Soc. de biol. **54**:201 and 300, 1902.

14. Bergstrand, H.: Ueber die akute und chronische gelbe Leberatrophie, Leipzig, G. Thieme, 1930.

15. Stewart, M. J.: Proc. Roy. Soc. Med. **10**:10, 1917. Turnbull, H. M.: ibid. **10**:47, 1917.

In keeping with previous experience, it is found that processes drained by the inferior mesenteric vein metastasize to the left lobe and that processes drained by the superior mesenteric vein metastasize to the right lobe.

The probable hemodynamic mechanism of this separation is discussed, together with the evidence for concluding that there are two relatively unmixed columns of blood flowing side by side in the portal vein: one from the superior mesenteric vein, and one from the compound splenic and inferior mesenteric vein.

CHEMICAL CHARACTER OF THE ENTEROCHROMAFFIN CELLS

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THIS paper is concerned only with the histochemistry of the enterochromaffin cells; for their morphologic character, histogenesis, distribution and possible functions the reader is referred to the comprehensive survey of Macklin and Macklin [1] and to the articles of Kull,[2] Hamperl,[3] Cordier [4] and Gillman.[5]

The granules of the enterochromaffin cells show a number of interesting tinctorial properties, which have invited considerable speculation regarding their chemical composition.

Their most important staining reactions are as follows:

1. The chromaffin reaction (Heidenhain [6]), shared by the cells of the medulla of the adrenal gland, consists in a brown staining of the granules by dichromates. This shade is due not only to the reduction of dichromate to chromic dioxide (CrO_2) but to the formation of colored oxidation products.[7] A similar reaction takes place if dichromate is added to an aqueous solution of epinephrine. With this observation as a starting point, Verne [8] took crystals of a number of related compounds and observed the formation of colors on the addition of dichromate. He found that all ortho- and para-dihydroxybenzenes and ortho- and para-aminophenols are chromaffin; i. e., they produce dark brown pigments when treated with dichromate. On the contrary, meta-dihydroxybenzenes and meta-aminophenols gave no reaction.

2. The argentaffin reaction consists in the reduction of an ammoniacal silver nitrate solution to metallic silver, with blackening of the granules.

From the Department of Medicine, University of Chicago.

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1. Macklin, C. C., and Macklin, M. T., in Cowdry, E. V.: Special Cytology, ed. 2, New York, Paul B. Hoeber, Inc., 1932, sect. 8.
2. Kull, H.: Ztschr. f. mikr.-anat. Forsch. **2**:163, 1925.
3. Hamperl, H.: (*a*) Ztschr. f. mikr.-anat. Forsch. **2**:506, 1925; (*b*) Virchows Arch. f. path. Anat. **286**:811, 1932.
4. Cordier, R.: Arch. de biol. **36**:427, 1926.
5. Gillman, J.: South African J. M. Sc. **7**:144, 1942.
6. Heidenhain, R.: Arch. f. mikr. Anat. **6**:368, 1870.
7. Gerard, P.; Cordier, R., and Lison, L.: Bull. d'hist. appl. **7**:133, 1930.
8. Verne, M. J.: Bull. Soc. chim. biol. **5**:227, 1923.

It should be made clear, as stressed by Cordier [9] and Hamperl,[8b] that the argentaffin reaction is fundamentally different from all other silver impregnations. In the argentaffin reaction it is a substance contained in the granules themselves that achieves the reduction (Masson-Fontana [10] technic), whereas in other silver impregnations an extra reducer, applied before or after the silver solution, is responsible for it. Misuse of the term "argentaffin" has resulted in considerable confusion. The argentaffin reaction, if performed correctly, possesses a marked chemical specificity, while silver impregnations in general are not specific in the chemical sense of the word, no matter how selective they may be for certain morphologic structures. Therefore, the only silver stains that can be considered selective for argentaffin substances are those which utilize the reducing power of those substances, without employing a secondary reducer. Before specificity for any other type of stain can be claimed, it must be shown conclusively by the use of consecutive serial sections that it stains exactly the same cells as the Masson-Fontana technic. It should be borne in mind that no silver stain is absolutely specific, and if the solution is applied long enough, an increasing number of structures will be stained until finally the entire section becomes uniformly black. Granules of leukocytes usually become impregnated simultaneously with the enterochromaffin cells, although in a lighter shade. They show all the other typical reactions of the enterochromaffin granules, but the shades are much less brilliant. They probably contain a compound identical with, or related chemically to, the enterochromaffin granules.

Fontana's solution must be prepared fresh, since it does not keep well; even in the course of the usual staining time a fine granular precipitate may be deposited all over the slide; also, by the time the granules are stained sufficiently dark the background may assume a fairly intense brownish shade. The latter cannot be removed by gold toning, as this will cause fading of the granules (Hamperl [8b]).

In an attempt to avoid the disadvantages of the Masson-Fontana technic a method was developed with which, as could be shown by the use of thin consecutive serial sections, exactly the same cells are stained as with the former, but in a much darker shade, while the background remains colorless. Precipitates are not formed.

Fix tissues in any aqueous fixative containing solution of formaldehyde U. S. P. Dichromates are better avoided, because they tend to cause a dark staining of the connective tissue. Treat deparaffinized sections for ten minutes to two hours with strong solution of iodine U. S. P. Bleach with thiosulfate or bisulfite. Wash sections thoroughly under the tap and rinse in distilled water. Impregnate for twelve to twenty-four hours at 37 to 45 C. in the following mixture:

9. Cordier, R.: Bull. d'histol. appliq. à la physiol. **4**:161, 1927.
10. Masson, M. P.: Compt. rend. Acad. d. sc. **158**:59, 1914.

Stock solution 1. To 100 cc. of a 3 per cent solution of methenamine U. S. P. add 5 cc. of a 5 per cent solution of silver nitrate. Shake until the initial heavy white precipitate disappears.

Stock solution 2. A fifth-molar borate buffer of p_H 7.8 to 8.2. To 100 cc. of a fifth-molar (1.24 per cent) solution of boric acid add 8 to 12 cc. of a fifth-molar (7.6 per cent) solution of sodium borate ($Na_2B_4O_7.10H_2O$). The use of solutions that are more alkaline hastens staining but impairs its selectivity. Both stock solutions keep indefinitely in the ice box.

For use mix about 25 cc. each of stock solution 1 and of distilled water and add about 5 cc. of stock solution 2.

When the enterochromaffin cells stand out black, rinse the slide thoroughly in distilled water, tone with a 0.1 per cent solution of gold chloride for ten minutes, wash and fix in a 2 to 5 per cent solution of thiosulfate. Counterstain as desired.

In case of overstaining, carefully differentiate the slide before gold toning in a solution containing 0.1 to 0.2 per cent of ferric ammonium alum and 0.5 per cent of sulfuric acid, followed by acid alcohol (0.5 to 1 per cent hydrochloric acid in 70 per cent alcohol). This treatment usually bleaches the background so completely as to make gold toning unnecessary.

If staining is continued much beyond twenty-four hours, a number of other structures will also be stained. At thirty-six hours the granules of leukocytes (first those of the eosinophils, later those of the neutrophils); around forty-eight hours the spermatozoa (figure 1 *A*), and finally, between forty-eight and ninety-six hours, the beta granules of the pancreatic islets of several species, especially those of man and the rat (fig. 1 *B*, *C* and *D*), become blackened. The staining of the islet cells is somewhat capricious, and this method is not recommended as a routine stain for their differentiation.

The number of known true argentaffin substances in paraffin-embedded tissues is limited and includes, besides polyphenols and certain poorly known aldehydes (elastic fibers), urates. Epinephrine is argentaffin only if the silver solution is applied to fresh tissue; there is no fixative known that will preserve it. The granules of the enterochromaffin cells are preserved by all aqueous fixatives containing solution of formaldehyde U. S. P. but are dissolved by all formaldehyde-free aqueous fluids and by alcoholic ones whether or not they contain formaldehyde.[11] This is an important point since Dawson[12] and Sharples[13] have used the Bodian method, which involves the use of an alcoholic fixative and the application of a secondary reducer for the demonstration of the enterochromaffin cells. Now, after Bodian's fixative has been used, all the typical reactions of the enterochromaffin cells become entirely negative. It is the more remarkable that, in spite of all this, after formaldehyde fixation Bodian's method will pick out exactly the same cells as the specific stains in the colon and in the small intestine, although in the stomach a number of additional cells

11. Hamperl.[8a] Cordier.[4]

12. Dawson, A. B., and Barnett, J.: Stain Technol. **19**:115, 1944. Dawson, A. B.: Anat. Rec. **91**:53, 1945.

13. Sharples, W.: (*a*) Anat Rec. **91**:107 and (*b*) 237, 1945.

are stained. These cells are scattered, sometimes in large numbers, mainly in the deep layers of the antral and fundic mucosa [18b] where, according to authors who have used the Masson-Fontana technic, enterochromaffin cells are absent in human material and in most animals. However, by the use of consecutive serial sections it can be shown that the overwhelming majority of the cells stained by Bodian's technic are also stained by the Masson method, but in the latter case the shade is so pale as to escape attention easily, especially in counterstained preparations. With the methenamine-silver method the cells are far more conspicuous, provided gold toning is omitted, and their shade

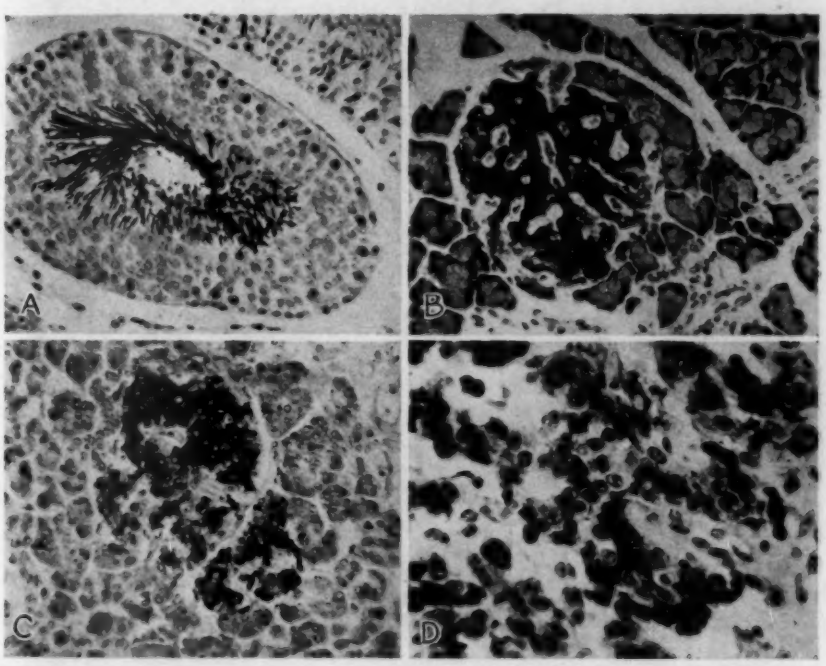

Fig. 1.—*A*, testis of the rat. Spermatozoa are stained black. *B*, pancreas of the rat. Only beta cells are stained; a group of peripheral alpha cells are unstained. *C*, human pancreas. Beta cells are stained. *D*, endocrine adenoma of pancreatic islets. Many dark beta cells are shown. All slides were stained with the silver-methenamine technic.

ranges from rich brown to brown-black. The same cells are demonstrated by all other specific stains to be mentioned later, but again the shade in which they show up is so pale that they are likely to be missed altogether unless slides without any counterstain are examined most carefully. These cells differ from the well known, typical enterochromaffin cells also in respect to their morphologic aspect, which is highly varied. Some of the cells are exceptionally small, polyhedral (fig. 2 *A*); others are elongated to 30 microns and more (fig. 2 *B*);

still others show bizarre star or spider shapes, with slender, tendril-like processes (fig. 2 *C* and *D*). Usually the nuclei, too, stain fairly intensely with silver.

The Popoff [14] stain on which an original theory of the nature and the physiologic role of the enterochromaffin cell is based is entirely nonspecific; it does not indicate any chemical relationship between the cells stained by it.

3. The azo reaction [15] consists in the production of brilliant reddish azo dyes when the section is immersed in the alkalized solution of a

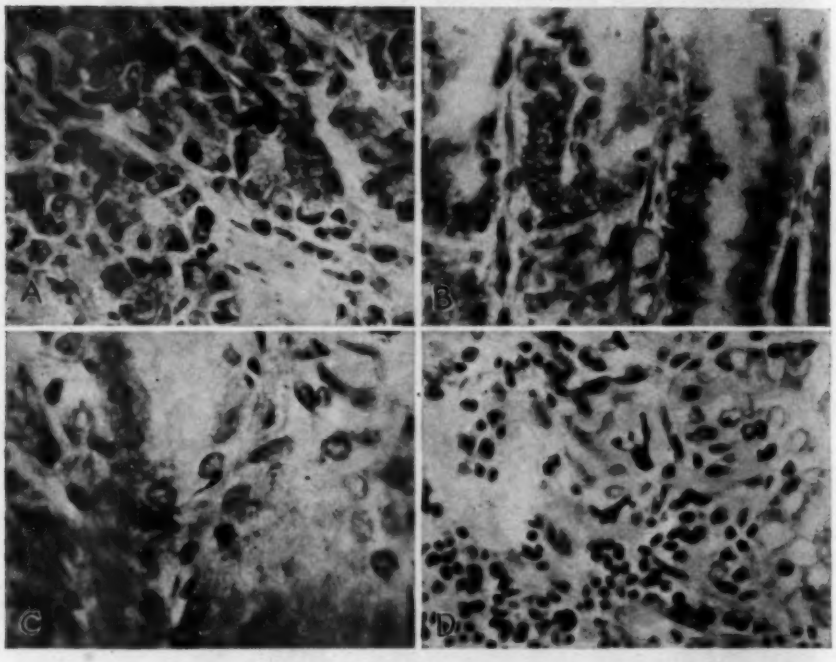

Fig. 2.—*A*, fundus of the human stomach. Three small polyhedral enterochromaffin cells are shown. *B*, antrum of the human stomach. An elongated cell may be seen. In *C* and *D* note the bizarre cells with processes. All slides were stained with the silver-methenamine technic.

diazotized amine. The reaction in this form is almost absolutely specific for phenols, and the shade produced depends partly on the nature of the amine used, partly on the structure and the complexity of the phenol. Simple phenols stain yellowish, more complex ones reddish or purplish.

4. The indophenol reaction [16] consists in the production of bluish indophenol dyes when the section is treated with dimethyl-p-phenylene-

14. Popoff, N. W.: Arch. Path. **27**:841, 1934.

15. Cordier, L., and Lison, L.: Bull. d'histol. appliq. à la physiol. **7**:140, 1930. Clara, M.: Ztschr. f. wissensch. Mikr. **51**:316, 1934.

16. Lison, L.: Arch. de biol. **41**:343, 1931.

diamine and an oxidant such as sodium hydrochlorite. This reaction is of limited practical usefulness, at least in vertebrate material, because the shade produced is too pale.

There are a number of other staining reactions [17] part of which are poorly understood chemically but are of sufficient interest to be mentioned.

5. With a very dilute solution of ferric chloride, the enterochromaffin cells assume a very pale greenish shade.

6. Certain oxidizing agents, such as nitric acid, bromine water and iodates, produce dark yellowish shades.

7. The enterochromaffin granules reduce ferricyanide to ferrocyanide; in the presence of ferric salts prussian blue is formed.

8. Clara [18] described a staining reaction with molybdate. In these studies it was found impossible to duplicate Clara's results.

9. A number of lake dyes (hematoxylin, brazilin, gallocyanin, gallamin blue, celestin blue, alizarin cyanin) when used in very dilute aqueous solution without the addition of a mordant stain the enterochromaffin granules sharply and selectively.[19]

10. The Mallory-Heidenhain azocarmine stain imparts to the enterochromaffin granules a brilliant ruby red to purplish or even bluish shade.[20] The results, although not consistent, are often superior to those obtained with any other stain, especially in cases of carcinoids.

11. Although not a staining reaction proper, it is felt that the fluorescence of the enterochromaffin cells [21] should be mentioned here.

On the basis of the staining reactions mentioned under points 1 to 5, Lison and Cordier [22] drew the following conclusions:

1. The enterochromaffin cells contain some ortho- or para-dihydroxybenzene.

2. Since the azo dyes formed are insensitive to alkali, the coupling must have occurred in the ortho position, which in turn means that the para position is not free, since coupling invariably occurs there whenever that position is free.

3. The group attached at the para position must be relatively simple because the shade of the azo dyes formed is yellowish.

A catechol compound with a short side chain in the para position would therefore show all the typical reactions of the enterochromaffin cell.

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17. Jonnard, R.: J. de physiol. et de path. gén. **32**:731, 1934.
18. Clara, M.: Ztschr. f. mikr.-anat. Forsch. **30**:467, 1932.
19. Clara, M.: Ztschr. f. Zellforsch. u. mikr. Anat. **22**:318, 1935.
20. Gomori, G.: Am. J. Clin. Path. **16**:115, 1946.
21. Erös, G.: Zentralbl. f. allg. Path. u. path. Anat. **54**:385, 1932.
22. Cordier and Lison.[15] Lison.[16]

The ideas of Lison and Cordier have been universally accepted and unchallenged up to this date.

There are, however, three weak points in Lison's reasonings which seem to have escaped the attention of subsequent workers.

First of all, the mere fact that the indophenol reaction is positive speaks against a para substituted phenol, since indophenol dyes, as a rule, do not form unless the para position is free. Second, derivatives of catechol and hydroquinone, such as epinephrine and homogentisic acid, respectively, are far stronger reducing agents than the granules of the enterochromaffin cell; they will reduce an ammoniacal silver solution almost instantly, whereas the granules require several hours. Third, the rule that para coupled azo dyes change their shade in alkaline solutions while those of the ortho coupled variety do not, is one to which there are numerous exceptions. Certainly no conclusions can be drawn from the fact that the shade of an azo dye is resistant to alkali.

A number of observations were made recently which cast considerable doubt on the correctness of Lison's ideas.

If Gibbs's reaction,[23] which consists in the formation of blue indophenol dyes when a phenol is added to the alkalized solution of 2,6-dichloroquinonechloroimine, is applied to sections, a distinct reaction is observed in the granules of the enterochromaffin cells. This reaction is negative with catechol and also with any para substituted phenol.

It can be shown that under the conditions of histologic technic the typical reactions of phenols are not the same as they are in the test tube. This difference, according to Coujard,[24] is due to the fact that phenols condense with formaldehyde to form insoluble bakelite-like resins. Therefore, he suggested, that, instead of doing simple test tube experiments, the conditions of histochemical technic should be duplicated by dissolving the substance in question in serum, writing a mark on a slide and treating the slide subsequently with all the reagents used in the histologic routine. From the results of reactions obtained on such slides valid histochemical conclusions can be drawn.

Substances to be tested are dissolved in a strength of 0.25 to 1 per cent in a mixture of equal parts of serum and 5 per cent gelatin. Marks are written with a clean pen dipped in the slightly warmed solution on a slide; more than twenty-five different substances can be tested on one slide. The slides are dried and subsequently exposed to fumes of a solution of formaldehyde U. S. P. in a closed jar for several hours; the excess solution of formaldehyde is driven off in the paraffin oven. The dry slides can be stored for weeks. For the test the slides are run through xylene and alcohols to distilled water and stained just as tissue sections would be.

By the use of this technic it can be shown that fixation accomplished in formaldehyde solution will render resorcinol and phloroglucinol just

23. Gibbs, H. D.: Chem. Rev. **3**:291, 1926.
24. Coujard, R.: Bull. d'histol. appliq. à la physiol. **20**:161, 1943.

as chromaffin as catechol is. Furthermore, catechol and hydroquinone reduce an alkaline silver solution within a few minutes while resorcinol and phloroglucinol take several hours to do so. Treating the slide for twelve hours with a 3 per cent solution of potassium iodate or dichromate almost completely abolishes the silver-reducing power of catechol and hydroquinone, while that of resorcinol, phloroglucinol and the enterochromaffin granules remains unimpaired. The Gibbs reaction, too, is intense with resorcinol but negative or negligibly positive with both catechol and hydroquinone. However, the most striking results are seen with the azo reaction. Certain diazotized amines will produce various shades when coupled with different phenols, and it is obvious that the shades obtained with resorcinol are invariably identical with those shown by the enterochromaffin granules while the shades obtained with catechol or hydroquinone are utterly different. Especially beautiful contrasts are obtained with the diazotate of nitroanisidine (trade name, "red B salt"), which stains resorcinol, phloroglucinol and enterochromaffin granules a fiery orange, and with the tetrazotate of p-p'-diaminodiphenylamine (trade name, "black B salt") which stains the same substances a deep maroon-red. Catechol and hydroquinone are stained in shades of pale ochre yellow by both reagents. Therefore, n the basis of these experiments it would seem that the histochemical reactions of the enterochromaffin cells are due to some derivative of meta-dihydroxybenzene (resorcinol) and not ortho-dihydroxybenzene (catechol), as it has been believed. This would be the more interesting as no resorcinol derivative has been known so far to be of physiologic importance in animals.

One more point should be mentioned briefly. Jacobson [25] has adduced excellent evidence to the effect that both enterochromaffin cells and tumors arising from them contain some pteridine compound. However, he also has made the statement that the typical reactions of the enterochromaffin cells may be due to the pteridine nucleus. This is definitely not the case, as can be shown by Coujard's technic; 2-amino-4-hydroxypteridine-6-carboxylic acid does not give a single one of the typical reactions. It was also impossible to confirm Jacobson's other contention that desoxyribose is present in the enterochromaffin cells.

SUMMARY

Contrary to previous ideas, the typical histochemical reactions of the enterochromaffin cells are due to the presence of a derivative of resorcinol. The presence of pteridine cannot be demonstrated in them with histochemical methods now available; they do not contain desoxyribose.

25. Jacobson, W.: J. Path. & Bact. **49**:1, 1939; Biochem. J. **40**:3 and 9, 1946.

TRIPLE SYNCHRONOUS PRIMARY CARCINOMA

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THE EARLIEST REPORT on multiple primary carcinoma was published by Billroth,[1] in 1869. He theorized that (*a*) each tumor must arise from its own parent epithelium, (*b*) each must present independent histologic cancerous characteristics and (*c*) each neoplasm must display its own metastatic spread. These criteria were so rigid that authentic instances of multiple primary cancers were necessarily excluded. The criteria proposed by Warren and Gates[2] were more flexible and more logical. They postulated that (*a*) each neoplasm must be histologically distinct, (*b*) each must reveal an obvious and definite picture of cancer and (*c*) the possibility of one tumor being a metastasis of another must be excluded. A review of the reported incidence of multiple primary cancers discloses a considerable degree of variation. Warren and Gates[2] computed the incidence from collected statistics, including the reported cases of Major,[3] Owen[4] and Ward,[5] as 1.8 per cent. Computed on the basis of their own series of cases the incidence was 3.7 per cent. Bilello and Montanini[6] found the rate to be only 0.5 per cent in a review of 8,024 autopsies, which included 1,154 cancers. Hurt and Broders[7] computed the statistical incidence as 3.34 per cent but reasonably argued that "15 of 2,033 patients with a single malignant tumor seen in 1929 will sometime later, in 1931, have another primary malignancy, and that therefore the actual incidence would be more correct at 4 per cent." Schreiner and Wehr[8] found, among 11,212 cases of cancer, an incidence of multiple carcinoma of 2.7 per cent. Bugher[9] studied 983 cancers, of which

From the Clinical Laboratory, Veterans Administration Hospital.

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1. Billroth, C. A. F., cited by White.[27]
2. Warren, S., and Gates, O.: Am. J. Cancer **16**:1358, 1932.
3. Major, R.: Bull. Johns Hopkins Hosp. **29**:223, 1918.
4. Owen, L. J.: J. A. M. A. **76**:1329, 1921.
5. Ward, R.: Brit. M. J. **2**:511, 1930.
6. Bilello, A., and Montanini, N.: Tumori **5**:369, 1931.
7. Hurt, H. H., and Broders, A. C.: J. Lab. & Clin. Med. **18**:765, 1933.
8. Schreiner, B. F., and Wehr, W. H.: Am. J. Cancer **20**:418, 1934.
9. Bugher, J. C.: Am. J. Cancer **21**:809, 1934.

3.1 per cent were multiple primary neoplasms. The highest incidence was reported by Burke,[10] who in a study of 583 cases found multiple cancer in 7.8 per cent. This unusually high incidence was explained by the fact that the cases were those in which postmortem studies had been made and all tissues examined. However, in a review of 10,870 autopsies, Kirshbaum and Shively [11] reported a low incidence of multiple cancers—1.77 per cent.

Multiple primary cancers may be synchronous (i. e., occurring at the same time) or metachronous (occurring at different times). Siegler and Silverstein [12] pointed out that most of the reported ones were metachronous, with an average interval of about three years between the discoveries of the neoplasms. Fried [13] mentioned that two or more cancers occurring synchronously are rare, synchronous occurrence being observed about once in a thousand autopsies. He believed that this rarity may be due to (1) a degree of immunity established by the first tumor and (2) the fact that a patient would be prone to succumb to one cancer before a second developed. The synchronous event of three primary cancers is indeed noteworthy. Shapiro and Bolker,[14] in reporting such a case, quoted Drooker's [15] analysis of the figures of Warren and Gates [2] to the effect that more than two primary cancers are observed in the same subject approximately once in 20,000 routine autopsies. However, in the enthusiasm of reporting triple cancers one may inadvertently overlook various sources of error, such as (1) types of cancer which commonly give rise to multiple lesions or are of multicentric origin (e. g., cancers of the skin, myeloma and hepatic carcinoma); (2) a bilateral neoplasm of the ovaries or the breasts; (3) carcinoma of the stomach or another portion of the gastrointestinal tract associated with carcinoma of the ovary; (4) the so-called carcinosarcoma, and (5) the teratoma. Authentic instances of more than two primary cancers occurring in the same patient have been reported by Herly,[16] McNamara,[17] Friedman and Golden,[18] Mayo,[19] Davis and associates,[20] Portuondo,[21] Kretschmer,[22] Willis,[23] Stout,[24] and Ewing.[25]

10. Burke, M.: Am. J. Cancer **27**:316, 1936.
11. Kirshbaum, J. D., and Shively, F. L., Jr.: J. Lab. & Clin. Med. **24**:283, 1938.
12. Siegler, S. L., and Silverstein, L.: Am. J. Obst. & Gynec. **52**:474, 1946.
13. Fried, B. M.: Arch. Path. **5**:565, 1928.
14. Shapiro, A. L., and Bolker, H.: Am. J. Cancer **40**:441, 1940.
15. Drooker, J. C.: J. A. M. A. **109**:1180, 1937.
16. Herly, L.: Arch. Surg. **9**:204, 1924.
17. McNamara, W. L.: J. Lab. & Clin. Med. **19**:269, 1933.
18. Friedman, A. B., and Golden, M. G.: Radiology **27**:497, 1936.
19. Mayo, C. W.: Proc. Staff Meet., Mayo Clin. **11**:165, 1936.
20. Davis, G. G.; Hanelin, H. A., and Mouzakeotis, T. C.: J. A. M. A. **106**:1359, 1936.

(Footnotes continued on next page)

About 10 per cent of the cases of triple primary cancers do not include the more usual cutaneous tumors. The case to be reported here, in which three primary synchronous carcinomas were encountered at autopsy, is worthy of recording.

REPORT OF A CASE

The patient was a 65 year old white man, who was well until eight months prior to entering the Veterans' Administration Hospital. He noticed increasing constipation. The stools were dark green but never black. He lost about 15 pounds (about 7 kilograms) within the eight weeks prior to his admission. Vomiting occurred two to three times in the week preceding admission, but there had been no hemoptysis. He complained of low abdominal and low back pain, which sometimes radiated to the left groin and occasionally to the right groin. At times the pain extended down the back of the left leg. At first this pain involved both legs, but at the time of admission it was limited to the left leg. His bowels had not moved in the six weeks prior to admission without an enema. A swelling had been noted in the left side of the neck about six to seven months before examination. A biopsy revealed metastatic carcinoma. His appetite had always been good until the present illness and then fell off rapidly. His left eye had been "running" more than the right. He complained of "sinus trouble," relieved by "running of his nose," which was present mostly in the wintertime. There had also been a cough, productive of three to four tablespoons of yellowish sputum per day. Moderate dyspnea was associated with the present illness. Other complaints were mild nocturia, especially when he drank a lot of fluid, and a chronic cutaneous condition which was diagnosed as hives and eczema. He was sensitive to string beans, corn, strawberries, tomatoes, fish, oysters and clams. His first wife died from "gangrene of the leg." He had been smoking two packs of cigarets a day. He said that he did not drink alcoholic beverages.

Physical Examination.—The patient appeared to be a poorly nourished, fairly well developed white man about the stated age of 65, chronically ill and showing evidence of marked loss of weight. A few small scattered excoriations were present over both legs. Many single and discrete small hard lymph nodes were felt in the left supraclavicular area. The eyes showed bilateral medial and external pterygia; there was slight clouding of the lenses bilaterally. The nose contained a mucoid discharge bilaterally, more on the right. The heart was not enlarged to percussion; the sinus rhythm was normal; there were no murmurs, shocks or thrills; the heart sounds were somewhat distant. The blood pressure was 128 systolic and 74 diastolic. The lungs were clear to percussion and auscultation; the expiratory phase of respiration was prolonged throughout. The abdomen disclosed no abnormality; no organs or masses were palpable. Rectal examination gave negative results. The right testis was smaller than the left. The muscles in the left thigh were flabby. In the left foot the pulses of the dorsalis pedis and

21: Portuondo, B. C.: Am. J. Cancer **28**:752, 1936.

22. Kretschmer, H. L.: J. Urol. **40**:421, 1938.

23. Willis, R.: The Spread of Tumors in the Human Body, London, Oxford University Press, 1934.

24. Stout, A.: Human Cancer, Philadelphia, Lea & Febiger, 1932.

25. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940.

posterior tibial arteries were depressed. Both ankle jerks were absent. The left knee jerk was depressed.

Laboratory Data.—Four examinations of the urine gave negative results. The blood coagulation time was 5 minutes; the bleeding time, ½ minute. Blood urea nitrogen was 27.4 mg., creatinine 3.1 mg., sugar 71 mg., cholesterol 166 mg., with cholesterol esters 100 mg., and total protein 6.3 Gm., with albumin 3.8 and globulin 2.5, per 100 cc. Alkaline phosphatase was 11.8 units on first determination; acid phosphatase, 1.5 units; on repeated determination alkaline phosphatase was 10.8 units. The icterus index was 5.5. The cephalin flocculation test was negative. The prothrombin level was 76 per cent; the hemoglobin content, 14.5 Gm.; a repeated estimate of hemoglobin showed 15.3 Gm. The first white blood cell count was 5,000; a second white blood cell count was 8,000, with 81 per cent polymorphonuclear cells and 19 per cent lymphocytes. The Wassermann and Kahn tests of the blood were negative. The blood sedimentation rate was 25 mm. in one hour. The stools revealed no occult blood. Proctoscopic examination gave negative results. Roentgenograms of the lumbosacral portion of the spinal column revealed considerable narrowing of the interspace between the fifth lumbar and the first sacral vertebra and hypertrophic changes of the contiguous surfaces. Roentgenograms of the skull disclosed several mottled areas of decreased density in the right half of the occipital bone, in the region of the eminence. This was compatible with early metastatic disease. A roentgenologic study of the gastrointestinal tract revealed a coarsened mucosal pattern of the duodenum, which probably represented duodenitis. In addition, the descending portion of the duodenum showed a small outpocketing along the left lateral margin, which represented a diverticulum. An intravenous pyelogram revealed no evidence of a primary renal neoplasm. Many roentgenograms of the chest were taken, and most of them demonstrated adenopathy of the lung roots in the paratracheal region.

Course.—The patient complained of constant severe pain of the lower part of the back from the time of admission to the time of his death. In spite of an intensive search, no primary focus of the metastatic carcinoma could be found.

Diagnosis.—Carcinomatosis, generalized, primary site undetermined; duodenitis and duodenal diverticulum.

Postmortem Examination.—The body was that of a well developed but poorly nourished white man. There were numerous visible and palpable large discrete firm lymph nodes in the left side of the neck. Metastatic tumor nodules were observed throughout the lower paravertebral muscles, the intra-abdominal lymph nodes, the para-aortic lymph nodes, the mediastinal lymph nodes, the left cervical lymph nodes, the right adrenal gland, the right kidney, the pelvic retroperitoneal tissue and the sacrum. The right lung weighed 710 Gm. and the left lung 630 Gm. Serial gross sections of the lungs showed no tumor, but sections were taken for microscopic study from all discolored or dense foci. The heart weighed 550 Gm. and showed moderate hypertrophy of the left ventricle. The coronary arteries and the aorta revealed considerable arteriosclerosis. The spleen weighed 250 Gm. and showed no tumor. The liver weighed 1,490 Gm.. There were no tumor metastases. The pancreas was normal. The prostate gland was enlarged. Repeated sections disclosed noncircumscribed, poorly outlined foci of dark grayish discoloration which were firm to hard in consistency. Permission to examine the skull and brain was not obtained. The thyroid gland was grossly normal. Repeated sections disclosed in the right lobe a minute indistinct grayish focus which was firm in consistency and which measured 4 mm. in diameter. The pharynx, the larynx and the structures of the mouth revealed no changes.

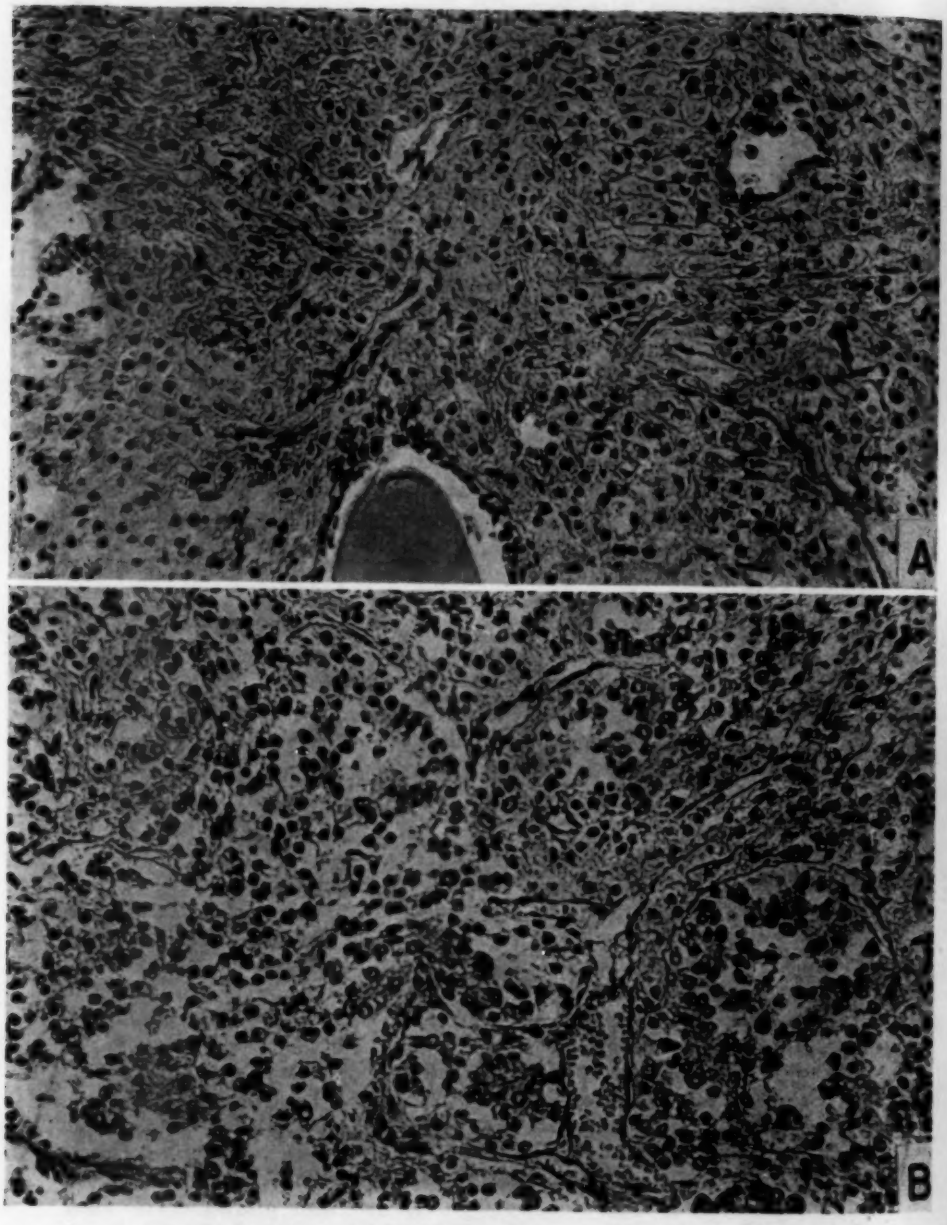

Fig. 1.—*A*, adenocarcinoma of the prostate gland; *B*, metastasis.

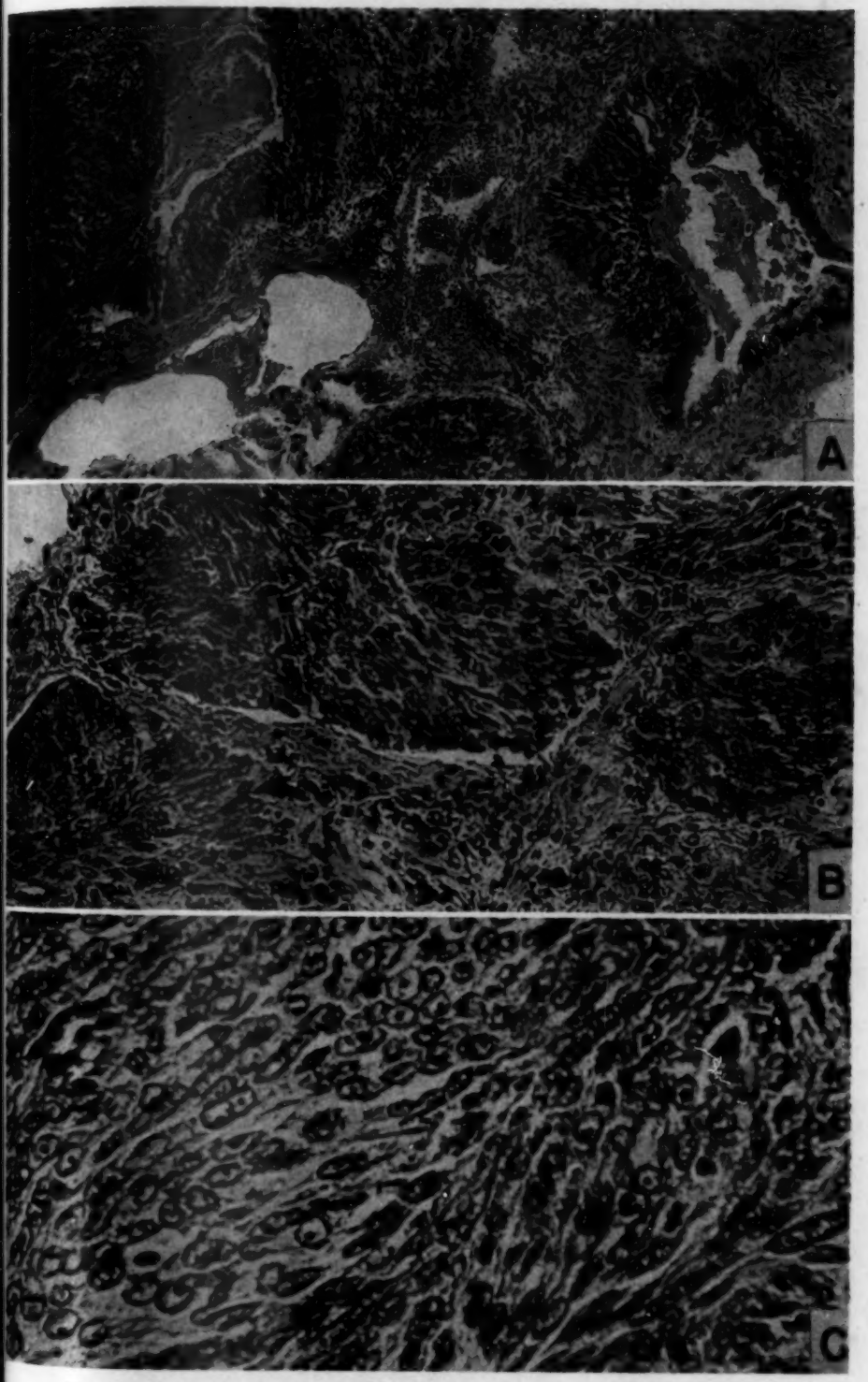

Fig. 2.—*A* and *B*, bronchogenic carcinoma of the lung; *C*, metastasis occurring in a cervical lymph node.

Microscopic examination of the metastatic tumors occurring in the mediastinum and the abdominal cavity revealed an ill defined glandular structure supported on a fine connective tissue framework. The cell type was small, round, with scant clear cytoplasm and a large round dark nucleus. There was considerable variation in size, shape and tinctorial affinity. Many nuclei were hyperchromatic, while a few were seen in mitosis. The tumors were divided into irregular lobules by connective tissue septums, which in turn were infiltrated by tumor cells (fig. 1*B*). The prostate gland was the seat of a neoplasm composed of small irregular glands lined by cuboidal cells with clear cytoplasm and small dark round nuclei. This was

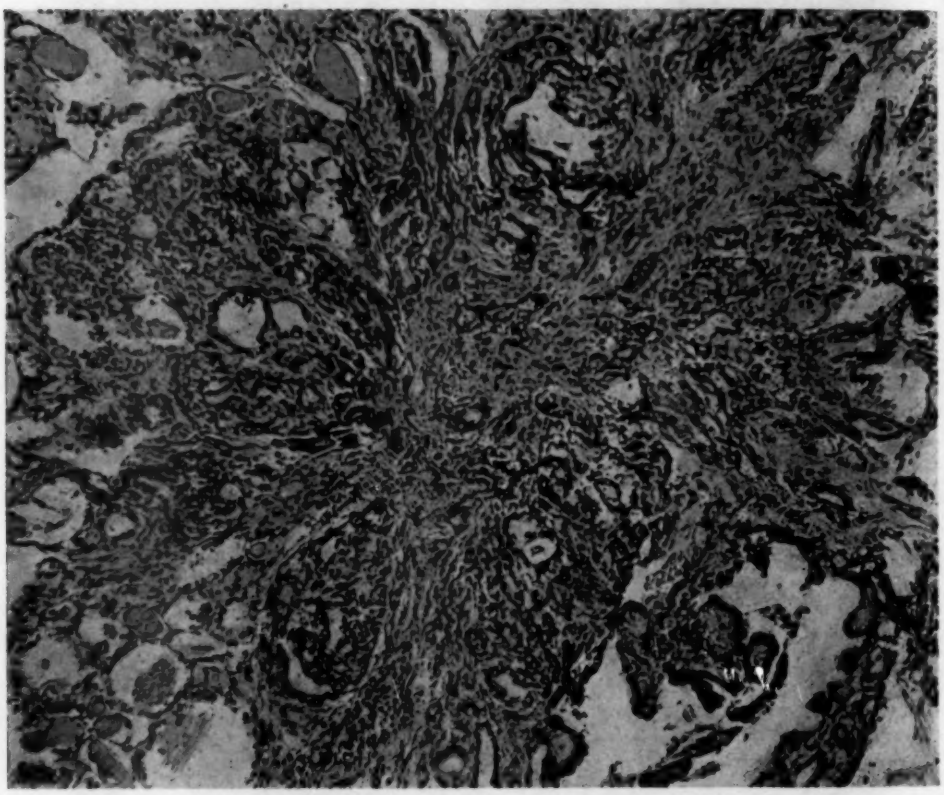

Fig. 3.—Papillary adenocarcinoma of the thyroid gland.

obviously the primary site of the metastatic carcinoma (fig. 1*A*). One of the sections of lung revealed a minute tumor composed of nests of plump spindle-shaped cells which could be traced directly to the cells lining a small bronchus. The tumor cells had granular cytoplasm and vesicular nuclei. They varied in size and staining reaction, and there were many mitoses. There was evident local infiltration as well as invasion of small venules. The structure of this tumor was that of an early bronchogenic carcinoma (fig. 2*A* and *B*) and quite different from that of the prostatic cancer or that of its metastases. Section of a cervical lymph node showed the node almost completely replaced by infiltrating

metastatic epidermoid carcinoma. The cells varied from polygonal to plump spindle form, with granular cytoplasm and vesicular nuclei. These sections were remarkably similar to those of the bronchogenic tumor (fig. 2*C*). A section of the small gray focus removed from the right lobe of the thyroid gland revealed a papillary tumor of atypical glandular structure. The cells were small and the nuclei hyperchromatic. Although the tumor had not invaded blood vessels, it presented the characteristic morphologic picture of a papillary adenocarcinoma of the thyroid gland (fig. 3).

Final Diagnosis.—Adenocarcinoma of the prostate gland metastasizing to the mediastinal, para-aortic and pelvic lymph nodes, the right kidney, the right adrenal gland, the paravertebral muscles, the pelvic retroperitoneum and the sacrum.

Bronchogenic carcinoma, epidermoid, metastasizing to the left cervical lymph nodes.

Papillary adenocarcinoma of the thyroid gland.

COMMENT

The absence of an obvious primary site of the metastatic carcinoma demanded careful serial sectioning of all the available organs. The reward was that two small carcinomas were discovered, one in the thyroid gland and one in a bronchus, in addition to a primary carcinoma of the prostate gland. Had the prostate gland been recognized clinically as the primary site of the metastasizing tumor, it is doubtful if the other two cancers would have been looked for or found. It is quite within the realm of probability that were all necropsies on patients with cancer performed with the purposeful intent of searching for other primary neoplasms, the incidence of such multiple tumors would be much higher than the average reported, 4 per cent.

The apparent rarity of multiple carcinoma has suggested that the development of one cancer endows the organism with some immunity against further development of other cancers. Peller [26] even suggested that it would be logical and feasible to induce experimentally a relatively benign and curable cancer of the skin to prevent the future development of more malignant tumors of other organs.

It is generally conceded, however, that cancers arise through the combined influence of two agencies: (1) an extrinsic environmental factor which is competent to stimulate cytogenesis and (2) a hereditary intrinsic factor of susceptibility or predisposition. White [27] has attempted to explain the genesis of multiple cancers on the basis of the interaction of a gene bearing the unit character for carcinoma inheritance with a gene bearing the unit character for localization, the latter endowed with the ability to affect various structures similarly. The interaction of these two genes necessarily takes place in an environment which is adequate to stimulate cytogenesis. I agree with

26. Peller, S.: Am. J. Hyg., Sect. A **34**:1, 1941; J. Hered. **35**:175, 1944.
27. White, J. W.: Am. J. Surg. **53**:71, 1941.

the implications of Warren and Ehrenreich [28] and of Warren and Gates,[29] that the incidence of multiple primary cancers is probably greater than formerly supposed and that it is sufficiently high for one to presuppose an increased individual susceptibility as its basis.

SUMMARY

Multiple primary cancers, exclusive of cutaneous tumors, are more common than is generally believed. Triple synchronous primary cancers are rarely reported. Systematic and well disciplined postmortem examinations would probably disclose many more multiple primary cancers than are found in the usual "routine" autopsies. The incidence of multiple cancers is sufficiently great to permit postulation of an increase of the subject's susceptibility to cancer.

A case of triple primary carcinoma is reported. The cancers were discovered during a search for the primary site of a tumor. They were diagnosed as: adenocarcinoma of the prostate with extensive metastases; epidermoid bronchogenic carcinoma metastasizing to cervical lymph nodes; papillary adenocarcinoma of the thyroid gland.

28. Warren, S., and Ehrenreich, T.: Cancer Research **4**:554, 1944.
29. Warren, S., and Gates, O.: J. A. M. A. **115**:1705, 1940; footnote 2.

Case Reports

CONGENITAL ANEURYSM OF AN AORTIC SINUS

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ANEURYSMS of the aortic sinuses are occasionally reported. The great majority of the reported ones have been of mycotic or syphilitic origin. Congenital aneurysms of the sinuses of Valsalva are rare. Study of the literature has revealed only 16 cases. Twelve concerned persons under 30 years of age. Rupture of the aneurysmal sac has been reported in 7 cases and occurred in a case which we shall report.

In 2 cases (those of Goehring[1] and Kawasaki and Benenson[2]) the aneurysm involved the posterior aortic sinus (the sinus from which no coronary vessel arises). In each of these cases the aneurysmal sac ruptured into the right atrium. In the latter case death occurred within a few minutes. In an additional case, reported by von Krzywicki,[3] the aneurysm involved the posterior portion of the right aortic sinus and ruptured into the right atrium. In the majority of cases the right aortic sinus was involved, with the sac extending into the right ventricle, although in 4 cases all 3 sinuses showed involvement.

We now report an additional case in which the posterior sinus was involved, with the sac rupturing into the right atrium.

REPORT OF A CASE

A 23 year old white man was admitted to the hospital, Nov. 14, 1946, with a chief complaint of substernal pain.

His usual good health had been interrupted by sudden onset of a tearing substernal pain, which radiated down both arms and was accompanied by sweat and

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1. Goehring, C.: J. M. Research **42**:49, 1920.

2. Kawasaki, I. A., and Benenson, A. S.: Ann. Int. Med. **25**:150, 1946.

3. von Krzywicki, C.: Beitr. z. path. Anat. u. z. allg. Path. **6**:465, 1889.

shock. This occurred on November 11, while he was sawing wood at his home. With rest, the pain in the arms disappeared, and the substernal pain became less severe.

A physician, called the following day, told him he had a "leaky heart." A fever of 102 F. was noted, but no chill. Penicillin was administered orally, and a hypodermic injection was given for relief of pain.

On admission the patient complained of the pain, which had been continuous, and of soreness in the upper part of the abdomen. The least exertion had caused dyspnea, and he volunteered that he had noticed reddish-colored urine that morning. The substernal pain did not radiate and was described as dull and constant. He complained of general malaise, nausea, feverishness and anorexia but said that there had been no cough, chills or vomiting.

The history was one of health, and no history resembling that of rheumatic fever was elicited. He had been discharged from the United States Navy ten months previously, and no murmurs had been noted at that time or at any of his previous physical examinations.

His recent health had not been marred by any infection of the upper respiratory tract, malaise or urethral discharge.

He stated that a brother died at the age of 23 with rheumatic heart disease. No autopsy was performed on this sibling, but the history obtained from the father was classically that of rheumatic heart disease.

Examination revealed a small but well developed white man, alert and cooperative, who appeared acutely ill and anxious. He was not orthopneic.

No petechiae, palpable lymph nodes, subcutaneous nodules or icterus was noted. The conjunctivas and mucous membranes revealed no lesions, nor did the fundus oculi. The lungs disclosed no physical signs of disease. The blood pressure was 156 systolic and 20-0 diastolic and equal in the two arms. A Corrigan pulse and a pistol shot femoral sound was observed, along with regular rhythm.

The heart was not grossly enlarged to percussion. There was a systolic thrill to the left of the sternum. To and fro murmurs were heard in all valve areas, but were loudest in the tricuspid valve area. These murmurs were best described as machinery-like and loud. There was no edema.

The liver was 4 fingerbreadths below the costal margin and tender. The spleen was not palpable.

The rest of the examination disclosed nothing remarkable.

An initial impression of subacute bacterial endocarditis with rupture of an aortic cusp was recorded, and blood cultures were ordered made twice daily, with penicillinase added to the mediums. The blood cultures, including those of arterial blood, were never positive. On admission the blood urea nitrogen was 25 mg. per 100 cc.; the white blood cell count was 26,000, with 1 myelocyte, 3 juvenile forms, 3 band forms, 65 segmented forms, 20 lymphocytes and 8 monocytes per 100 cells; the red cell count was 4,800,000, with 14 Gm. of hemoglobin per 100 cc.; the urinalysis and the Kahn test of the blood gave negative results; the erythrocyte sedimentation rate was 12 mm. in one hour (Cutler).

The admission roentgenogram of the chest (at 6 feet [about 2 meters]; 14 by 17 inches [35.5 by 43 cm.]) revealed a cardiac contour comparable to that seen in cases of rheumatic heart disease. It appeared to be enlarged in all diameters, and there was straightening of the upper left border. There were minimal congestive signs, and the costophrenic angles were clear.

The admission electrocardiogram revealed depression of the ST segments in leads 2 and 3 and inverted T_3 (fig. 1). The changes noted were nonspecific but significant.

The patient continued to have a low grade afternoon fever but ate well. The substernal pain was controlled with meperidine hydrochloride ("demerol hydrochloride").

Penicillin was withheld because of the desire to ascertain the sensitivity of the organism which, it was felt certain, was present but which could not be cultured.

The patient's condition remained good. His temperature was 98 F., and he ate well. The white blood cell count dropped to 11,600, with 74 segmented forms, 21 lymphocytes and 5 monocytes per 100 cells.

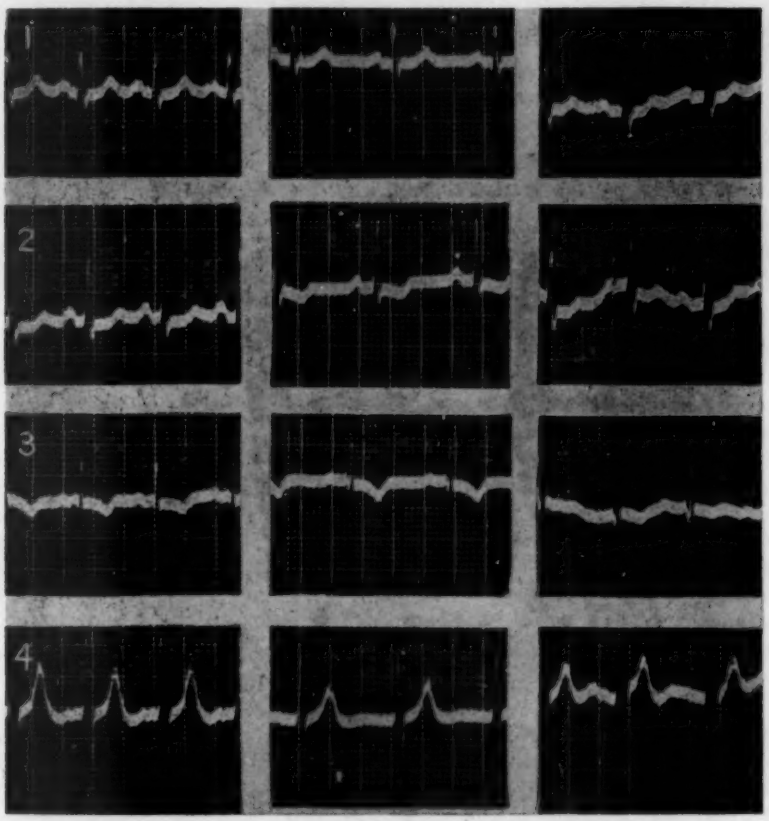

Fig. 1.—Electrocardiograms showing nonspecific but significant changes: Those at the left, taken on November 14, show sinus tachycardia. P-R is 0.14. The ST segment is slightly depressed in leads 1, 2, 3 and 4. The T waves are upright in leads 1, 2 and 4 and inverted in lead 3. T_4 is somewhat peaked. Conclusion: The ST depressions suggest coronary insufficiency; however, there is no definite evidence of myocardial damage.

The electrocardiograms in the middle, taken on November 20, show sinus rhythm. P-R is 0.16. The ST segment is slightly depressed in leads 2 and 3. The T waves are upright in leads 1 and 4 and inverted in leads 2 and 3. Conclusion: Since the previous tracing, the ST has returned to the isoelectric line in leads 1 and 4. T_3 is now inverted and T_4 lower.

The electrocardiograms at the right, taken on November 28, show sinus tachycardia. P-R is 0.16. The ST segment is slightly depressed in lead 1 and elevated in lead 4. The T waves are upright in leads 1, 2 and 4. Conclusion: T_3 is now upright again and ST_4 elevated.

On November 18 it was noted that dyspnea had become progressive during the night, and rales were noted in the bases of both lungs. The venous pressure was 240 mm. of mercury on that date, and pressure applied in the right upper quadrant of the abdomen effected a rise to 290 mm. The arm to tongue circulation time was twenty-six seconds (sodium dehydrocholate) and the arm to lung time was five seconds (ether). On November 18 a roentgenogram revealed cardiac dilatation and pulmonary congestion.

Because of the change in the patient's condition, he was digitalized with the whole leaf in twelve hours, and penicillin was administered, 100,000 units every three hours, despite the absence of a positive report on the blood culture. (He was maintained on 2 cat units of "digalen" a day, injected intramuscularly.)

Coughing, dyspnea, anorexia and vomiting began and became most exasperating. He was given mercurial diuretics for the pulmonary edema, with no improvement despite diuresis. On November 23 flatness was noted in the right side of the chest, and thoracentesis produced 500 cc. of sterile straw-colored fluid. This procedure considerably relieved the respiration. However, his course continued downhill, and thoracentesis of the right side was performed again on November 24, with removal of 640 cc. of fluid. This fluid revealed a total protein content of 1.4 Gm. per 100 cc. The penicillin blood level was 0.5 unit before a dose and 2 units after a dose. A roentgenogram made with portable x-ray apparatus on November 25 revealed pulmonary congestive changes and hydrothorax of the right side.

The blood urea nitrogen had risen to 45 mg. per 100 cc. by November 26, and the carbon dioxide–combining power was 45 volumes per 100 cc. An increase of intensity was noted in the murmurs over the tricuspid area on this date. On November 28 the patient's condition was critical, and 1,200 cc. of fluid was removed from the right side of the chest. He coughed up blood-streaked sputum. Daily electrocardiograms were virtually unchanged from that taken on admission except that T_3 and T_4 had become inverted on the second hospital day. He had been maintained on 2 cat units of "digalen" intramuscularly every day. The blood urea nitrogen mounted to 51 mg. per 100 cc.; the carbon dioxide–combining power remained normal. Cyanosis developed and was progressive; the respiration continued rapid despite continuous administration of oxygen, and the patient died on November 29.

Autopsy.—The postmortem findings were virtually those of a cardiac abnormality with acute congestive failure. There was approximately 1 liter of straw-colored fluid in the right thoracic cavity. The lungs together weighed 1,355 Gm. The pleural surfaces were smooth. Cut section of the lungs revealed a uniform pink color with minimal black mottling. Crepitation was somewhat decreased, and the bronchi contained a minimal amount of frothy fluid.

The heart weighed 385 Gm. There were minimal epicardial fat and a few subepicardial petechiae. The coronary arteries were patent. The myocardium appeared somewhat dark but was of normal thickness and consistency. There was an inadequacy of the posterior sinus of Valsalva, which contained a defect, 1 cm. in diameter, that was continuous with a saccular outpouching into the right atrium (fig. 2 *A* and *B*). This sacculation was at the annulus fibrosus along the anterior portion of the medial leaflet of the tricuspid valve (fig. 3). The sac formed measured roughly 2 cm. in diameter and had an estimated volume of 10 to 12 cc. It opened widely into the atrium. All valves were otherwise unremarkable. The chordae tendineae appeared normal. The foramen ovale was closed. The interventricular septum was intact. No other cardiac anomalies were noted.

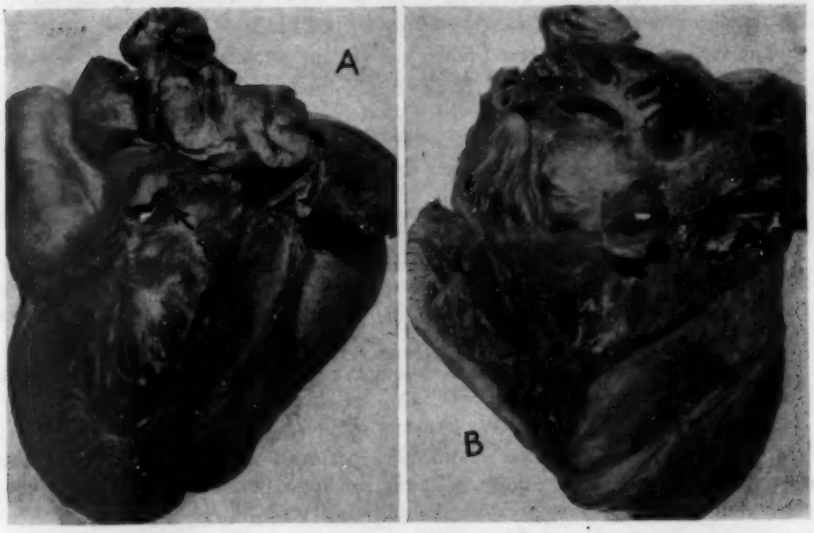

Fig. 2.—*A*, view of heart, showing the defect in the posterior aortic sinus. (Specimen retained in the collection of the Naval Medical School, no. 30718.)

B, view of the right side of the heart, showing a saccular outpouching from the sinus defect, which involves the annulus fibrosus of the tricuspid valve and protrudes into the right atrium.

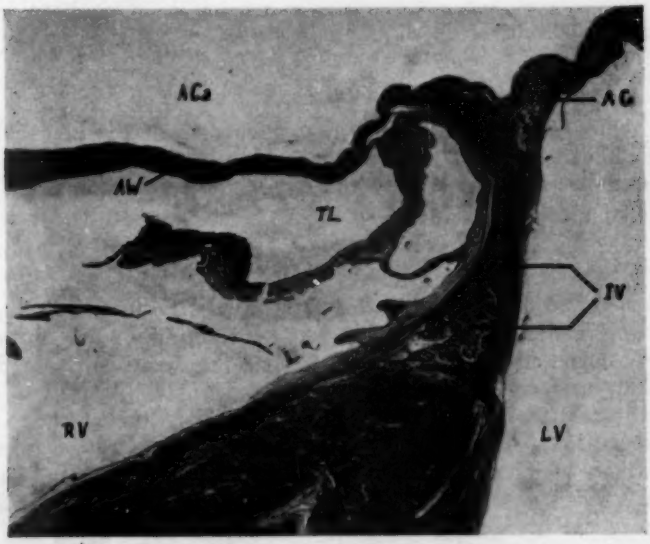

Fig. 3.—Photomicrograph of the wall of the aneurysm and the related adjacent structures: *LV*, left ventricle; *RV*, right ventricle; *IV*, interventricular septum, membranous and muscular portions; *AC*, aortic cusp; *TL*, tricuspid leaflet; *AW*, aneurysm wall; *ACa*, aneurysm cavity.

The pulmonary artery contained no thrombus. The thoracic aorta was smooth. All measurements of the heart were within normal limits.

The sac and the cardiac blood failed to yield any organisms on culture.

The liver weighed 1,700 Gm. It was dark in appearance, and the central markings were distinctly seen through the smooth, thin capsule. The consistence was normal, and cut section showed prominent yellowish brown parenchyma, with deep central areas forming a marked nutmeg mottling throughout. The biliary tract was unremarkable.

The other organs grossly appeared normal.

Microscopic Examination.—The epicardium showed a moderate amount of adipose tissue. The myocardial cells were somewhat increased in size, and their nuclei were often large and pale. The endothelial cells were moderately swollen and assumed a cuboid appearance.

Sections of the aneurysm projecting into the right atrium showed it to consist chiefly of fibrous tissue. Some places showed shreds of remaining elastic fibers. No inflammatory cells were present in any of the sections studied.

The aorta showed moderate endothelial hyperplasia of the vasa vasorum. This change was noted generally in many of the smaller arteries. However, there was no evidence of inflammatory reaction in the vessel walls.

In the lungs, the interstitial tissue was edematous and in areas contained large numbers of neutrophils. In some areas the alveoli contained edema fluid. The endothelial cells lining the blood vessels were vacuolated and increased in number. Some of the smaller vessels were thrombosed. In some areas there was moderate emphysema. The alveolar epithelium was prominent in places. The bronchi were unremarkable.

The spleen showed hyperplasia of the littoral cells of the sinusoids.

The other organs were unremarkable except for the unexplained hyperplasia of the endothelial cells of the smaller vessels.

SUMMARY

A case of rupture of a congenital aneurysm of the posterior aortic sinus is described. We were fortunate in obtaining more clinical data than have been previously reported in these conditions. The case is reported also for its rarity.

COMMENT AND CONCLUSIONS

The absence of a syphilitic history and the failure to find gross or microscopic evidence of an inflammatory reaction in the aorta or the aneurysm lead one to the conclusion that the aneurysm was due to a congenital malformation of the posterior sinus of Valsalva, with an inherent weakness permitting gradual dilatation during the course of the patient's life. This is substantiated by the result of the microscopic examination, which failed to reveal any evidence of a recent or an old inflammatory process. Further, the gross and microscopic examinations failed to reveal any evidence of long-standing cardiac strain.

In view of the rapid clinical course following the onset of the patient's illness and the acute nature of the congestive failure, supported by the autopsy observations, it is felt that the rupture of the sac occurred at

the onset of symptoms. The subsequent congestive failure is attributed to the rupture rather than to tricuspid insufficiency due to aneurysmal obstruction.

From the clinical point of view this condition should be added to those which are considered in the differential diagnosis of myocardial infarction, ruptured aortic cusp and dissecting aortic aneurysm. Previous good health of the patient, nonspecificity of the electrocardiogram, a young age group and a machinery-like murmur of great intensity would aid in producing a suspicion of this condition.

Laboratory Methods and Technical Notes

MODIFIED EOSIN COUNTERSTAIN FOR FORMALDEHYDE-FIXED TISSUES

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THE EOSIN counterstain of routine hematoxylin-eosin preparations of tissue fixed in formaldehyde solution U. S. P. is, as a rule, inferior to that obtained with material fixed in Zenker's solution. Even though the staining is prolonged, the eosin usually is pale, has a washed-out appearance and frequently is confined to the periphery of the section. This is especially true for brain tissue. The eosin preparation described below stains rapidly and allows careful, uniform and controlled differentiation.

METHOD

1. Deparaffinize sections.
2. Stain in Harris or aqueous alum-hematoxylin 10 minutes.
3. Wash in tap water five minutes.
4. Differentiate in acid alcohol (1 per cent hydrochloric acid in 70 per cent alcohol U. S. P.) until pink.
5. Wash in tap water five minutes.
6. Place in ammonia water until nuclei are blue.
7. Wash in tap water five minutes.
8. Counterstain in the following solution one-half minute:

Eosin	1 Gm.
Potassium dichromate	0.5 Gm.
Saturated aqueous trinitrophenol	10 cc.
Absolute alcohol	10 cc.
Distilled water	80 cc.

9. Rinse in tap water two to three minutes.
10. Differentiate slowly in three changes of absolute alcohol.
11. Clear in xylene, mount in "permount" (Fisher Scientific Company).

RESULTS

Nuclei are stained blue; cytoplasm, muscle fibers and connective tissue, pale pink; red blood cells, yellow or orange.

From the Department of Pathology, Yale University School of Medicine.

General Reviews

LYMPHOID DISEASES

Hodgkin's Granuloma, Giant Follicular Lymphadenopathy, Lymphoid Leukemia, Lymphosarcoma and Gastrointestinal Pseudoleukemia

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THE TERM "lymphoid diseases" is used to designate a group of interrelated lesions composed of Hodgkin's disease (lymphogranulomatosis), giant follicular lymphadenopathy, lymphoid leukemia, lymphosarcoma and the gastrointestinal so-called pseudoleukemia of Briquet. All of them are initiated by hyperplasia of lymph follicles. In the majority of cases, they are preponderant or, if one prefers the term, "primary" diseases of the deeper lymphoid structures, including the abdominal lymph nodes or the abdominal and thoracic nodes combined, the spleen, the thymus and the gastrointestinal tract. Enlargement of the superficial nodes, if it occurs at all, is seldom preponderant or "primary" but a later development.

HODGKIN'S DISEASE

In 1832 Thomas Hodgkin called attention to a disease characterized by progressive enlargement of the lymph nodes associated with enlargement of the spleen. His paper was published under the caption "On Some Morbid Appearances of the Absorbent Glands and Spleen." Hodgkin's observations remained unnoticed until 1856, when Wilks directed attention to them and deplored the fact that Hodgkin had not included them under a distinguishing name. According to Hale-White, Hodgkin "owes his celebrity to the chivalrous honesty of Wilks." In 1865 Wilks published a paper entitled "Cases of Enlargement of the Lymphatic Glands and Spleen (or, Hodgkin's Disease)." In this manner the honesty of Wilks was again exemplified, and the eponymous accolade was conferred on Hodgkin a year before his death, which occurred at Jaffa, Palestine, in April 1866.

SYNONYMS

Hodgkin's disease is referred to under a host of names, Wallhauser (1933) having collected a series of fifty-two. Among the most confusing

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is "pseudoleukemia," which still is the prevailing German synonym. "Lymphadenoma" is the choice of many British writers, although the British are coming to use more the noncommittal title "Hodgkin's disease." In this country "Hodgkin's granuloma" and "Hodgkin's disease" or "lymphogranuloma" and "lymphogranulomatosis" seem to be the most popular.

DIFFERENTIATION

Of the 7 cases described by Hodgkin, some were almost certainly instances of varieties of lymph node tuberculosis, lymphoid leukemia or lymphosarcoma. That at least one of them was an example of the condition which is known as Hodgkin's disease was shown a century afterward by Herbert Fox. He examined a lymph node which had been given to him from Hodgkin's original collection at Guy's Hospital. In the node he demonstrated the histologic changes which are universally accepted as those of Hodgkin's disease.

During a period of sixty-four years after the appearance of Hodgkin's paper the disease came to represent an apparently hopeless conglomeration of lymph node and splenic enlargements. Perhaps the first attempts to solve the problem were made by Hughes Bennett and, one month later, by Virchow, who thus almost simultaneously established the independence of lymphoid leukemia. In time other lesions were eliminated and more properly classified elsewhere, so that in recent years Hodgkin's disease has assumed a place as an entity. It has been repeatedly shown that the disease is characterized by changes in the lymph nodes and elsewhere manifested by a connective tissue reticulum supporting variable numbers of lymphocytes and plasma cells, together with mononuclear and multilobular or multinuclear giant cells, with or without an admixture of eosinophils and eosinophilic myelocytes, and, on occasions, by areas of necrosis. There is some difference of opinion concerning the origin of the giant cells, but the histologic composite is nevertheless universally accepted as the criterion on which the diagnosis of Hodgkin's disease may be made. Incidentally, it is often forgotten that the giant cells of Hodgkin's disease were described by Greenfield in 1878, twenty years later by Sternberg (1898) and still later by Reed (1901-1902). They are almost always referred to as Sternberg's giant cells or as Reed cells and are practically never designated in such manner as to honor the name of the man who discovered them.

DISSEMINATION

In perhaps the majority of cases of Hodgkin's disease, the changes are confined to the lymph nodes or to the lymph nodes and the spleen. In some instances the disease brings about changes in auxiliary lymphoid depots in the connective tissue framework of practically every organ of the body, including the thyroid gland, the prostate, the lungs, the

kidneys, the liver, the bone marrow and the adrenal glands, the walls of the larger blood vessels, notably the portal and splenic veins, the subcutaneous fat tissues, the lymph nodules that are embedded in the mesentery and the omentum, the testicle, the serous membranes and the dura mater. The growths may press on and invade skeletal muscles, the heart, bone, the walls of blood vessels and other tubular structures, the lungs and the parenchyma of the solid viscera, nerve trunks, the soft tissues of the brain and spinal cord and elsewhere. Other opinion holds that Hodgkin's disease is a metastasizing malignant neoplasm, the primary growth occurring in the lymph nodes, according to one view, or in the bone marrow, according to another. Although Reed refers to "metastasis" and "metastatic nodules," she nevertheless concludes that the changes are those "suggesting a chronic inflammatory process."

INCIDENCE

Hodgkin's disease occurs most frequently between the ages of 20 and 40. It has been described as observed in the first year of life and in the seventieth. It is commoner in men than in women in the proportion of about 2 to 1. Its distribution is wide.

POSSIBLE ETIOLOGIC AGENTS

Tubercle Bacilli.—The view that Hodgkin's disease is a form of tuberculosis has been advanced on the grounds that:

> . . . Hodgkin's disease and tuberculosis are often found in the same patient; that there is frequently a family history of tuberculosis; that acute tuberculosis often develops in patients about to die of Hodgkin's disease; that there is a facultative symbiosis between the human tubercle bacillus and the unknown etiological agent of Hodgkin's disease; that lymphocytes act on the tubercle bacillus in such fashion as to alter its ability to produce the classical picture of tuberculosis producing instead, the peculiar histological picture of Hodgkin's disease; that Hodgkin's disease is caused by a degenerate form of the tubercle bacillus in which this degenerate perhaps passes over into a diphtheroid type that is practically a distinct species; that Hodgkin's disease is a neoplastic process in which tuberculosis plays the part of an excitant, . . .

Ewing (1940) states that "tuberculosis follows Hodgkin's disease like a shadow." This statement is widely quoted—largely, it would seem, because few pause to reflect on its factual flaws. From it, one might be tempted to believe that every sufferer from Hodgkin's disease suffers also from tuberculosis with the regularity with which a shadow follows its object and that tuberculosis is the one constant causative factor in the production of Hodgkin's disease. It is known that Hodgkin's disease and tuberculosis may occur in the same body and even in the same lymph node just as Hodgkin's disease and, for example, deposition of amyloid substance may occur in the same lymph node.

However, it is also known that tuberculosis may be found in association with a number of conditions other than Hodgkin's disease without the implication of cause and effect. On the other hand, there are those who seem willing to accept a compromise—that although every effort to prove, on the basis of bacteriologic and experimental evidence, that Hodgkin's disease is of tuberculous nature have thus far failed, the histologic changes nevertheless indicate that the lesion is tuberculous. Pathologists are agreed that in some cases of Hodgkin's disease necroses occur and that on occasions multinuclear giant cells of the Langhans variety may be found in or close to the areas of necrosis. In tuberculosis the giant cells are responding to living tubercle bacilli, and without special methods of staining the bacilli in them are invisible. Other minute, but inanimate, foreign bodies often produce giant cells of the Langhans type—in both instances these cells are reacting to insoluble foreign material, either living or dead. However, it may be assumed that every pathologist is capable of distinguishing between giant cells present because of living but invisible tubercle bacilli and giant cells arranged around relatively coarse and easily visible inanimate foreign body inclusions. The latter cells bear only a remote resemblance to the giant cells of tubercles and could scarcely be confused with them.

Andrews, of London, who, following the English custom, uses the word "lymphadenoma" synonomously with the term Hodgkin's disease, and "lymph gland" synonomously with "lymph node," summarizes his views in the following words:

> . . . The discovery of indisputable tubercle bacilli—the production of tuberculosis in a guinea pig by inoculation of portions of a gland with due aseptic precautions—these are positive evidences which naturally cannot be gainsaid. They prove that a given gland is tuberculous, but they do not disprove the possibility of its being also lymphadenomatous. Herein, I think, lies the fallacy into which those have fallen who have relied on animal experiment as establishing the identity of the two conditions. Their argument is this: "Here is a gland which, on microscopic and clinical evidence, you pronounce lymphadenomatous. I inoculate it into a guinea-pig, and behold! the animal develops tubercle. Therefore lymphadenoma is tubercle."

From the available evidence, the view that the changes in Hodgkin's disease are tuberculous appears to have been predicated on defective premises.

Brucella.—Forbus (1942) has carried out experimental investigations on the possible relationship of Hodgkin's disease and Brucella infection. His results are interesting, informative and suggestive. He states:

> . . . Extended studies on the incidence of the antemortem recovery of Brucella in 24 typical cases of Hodgkin's disease yielded the following results: Brucella was recovered in 9 of 17 cases of culture of the blood and in 9 of 23 cases of culture of excised lymph nodes; in 4 of 23 cases both blood and node culture yielded Brucella, and in 14 of 24 cases either blood or node culture yielded Brucella.

Coincident with the studies on cases of Hodgkin's disease, a series of 84 cases of lymphadenopathy, not Hodgkin's disease, was studied by the same cultural methods. In 7 of the 84 cases either blood or node culture yielded Brucella.

The strains of Brucella obtained at autopsy have been employed in a study of experimental brucellosis in a variety of animals, including guinea pigs, rabbits, dogs and hogs. These animals react to intravenous and intraperitoneal inoculations by the production of granulomatous lesions in the peritoneum, and especially in the lymph nodes. The lymph node lesions, particularly in the hog and the guinea pig, are characterized by extensive proliferation of the reticuloendothelial cells, sometimes so pronounced as to replace almost completely the lymphoid structures. The reaction is sometimes followed by necrosis and is always accompanied by outpouring of eosinophils and plasma cells. Multinucleated giant cells are typical of the fully developed lesions. In principle and in some of the details the reaction resembled that of Hodgkin's disease.

Leukotoxins.—Flexner conducted experiments to determine what changes would develop if leukotoxic serums derived from the lymph nodes, the spleen and the bone marrow were injected into animals. If at the time Flexner entertained any thought that his results might throw some light on the histogenesis of Hodgkin's disease, he gives no intimation of that fact in his publication. Nevertheless, the changes which occurred in the lymph nodes and the spleen and perhaps in the bone marrow of rabbits and guinea pigs were such as to suggest a sort of parallelism with changes occurring in the same situations in Hodgkin's disease in man, brought about in both instances possibly by toxic substances of cellular origin. Flexner's experiments showed that splenotoxin injected into guinea pigs produced marked enlargement of the lymph nodes, due to increase in the size of the follicles. In some instances the entire node was converted into the large clear cells which characterize the germinal centers. The spleen showed a mild degree of hyperplasia of the malpighian follicles. In the bone marrow multinuclear giant cells were present but apparently in reduced numbers. In guinea pigs receiving lymphotoxin the most striking alteration of the lymph node was found in dimensional hyperplasia of the lymph follicles, which was accompanied by lymphoid hyperplasia throughout the rest of the node, while the changes in the spleen were limited to increased size of the malpighian follicles. In the bone marrow "giant cells with multiple convoluted nuclei were abundant." In rabbits receiving myelotoxin the lymph nodes were increased in size, an increase due practically exclusively to multiplication of lymph follicles. Giant cells of nondescript type were not infrequently seen, and in some instances they were relatively numerous. The spleen was enlarged by increase of size of the malpighian bodies, to such an extent that the pulp was greatly reduced. It might be enlightening if Flexner's experiments were repeated and expanded with the object of reproducing Hodgkin's disease in those lower animals in which a disease apparently identical with or closely related to it is known to develop—dogs, horses, swine, sheep and other species. An

experiment of the latter sort was carried out by Cunningham (1925), who transplanted lymph nodes from a patient with Hodgkin's disease into the subcutaneous tissues of a chimpanzee. The animal remained well for a period of two years; he was then transferred to the menagerie of a circus and at the end of another two years was still apparently healthy. Symmers was unsuccessful in attempting to reproduce Hodgkin's disease in guinea pigs and rabbits by subinguinal injections of freshly emulsified lymph nodes.

NATURE OF HODGKIN'S DISEASE

There are two theories concerning the nature of Hodgkin's disease: one that it is a process of myeloidization of hyperplastic lymphoid tissues (Symmers), possibly due to a virus infection; the other that it is a primary malignant tumor either of lymph nodes (Mallory, 1914) or of the bone marrow (Medlar, 1931). In any event the first observable change occurring in the lymph nodes consists in numerical or dimensional hyperplasia of the lymph follicles, or both. The hyperplastic follicles may disappear early, or the hyperplasia may be found in company with the more advanced histologic changes. When the former occurs alone, it may be a source of error in the determination of the nature of the process, since the hyperplastic follicles are similar to or identical with those found in the same situations in giant follicular lymphadenopathy and other lymphoid diseases and in evanescent follicular lymphomas associated with various inflammatory conditions, as well as in lymph nodes draining the wastage from ulcerative new growths. Similarly, in the liver, the kidney, the bone marrow and other tissues the first observable histologic change in Hodgkin's disease consists in the appearance of small lymphomatous foci indistinguishable from those encountered in the same situations in several related diseases. It is only when histologic developments have advanced beyond this point that differentiation is possible.

The bone marrow may present several types of alteration in Hodgkin's disease. In one group of cases there is overgrowth of connective tissue, resulting in obliteration of the marrow cavity. This may involve different parts of the marrow system, or it may be limited to focal distribution in individual bones. In a second group the marrow is the seat of histologic changes of the same character as those encountered in the lymph nodes and elsewhere, which apparently arise on the basis of hyperplasia of the lymphoid foci normally resident in the bone marrow. There is a third group of cases attended by hyperplastic changes in the cells of the marrow, the increase affecting principally the myelocytes and eosinophils and the nongranular mononuclear giant cells or hemocytoblasts. The megakaryocytes are not noticeably increased and may even be conspicuously diminished. The latter fact

may be explained by the circumstance that megakaryocytes occur in such numbers in the tissues outside the osseous system as to impoverish the supply in the marrow, where at best they are not numerous. On the other hand, Bunting (1911) and Symmers (1924) found that megakaryocytes are sometimes present in apparently excessive numbers. Krumbhaar has recorded a case of Hodgkin's disease in which necropsy revealed characteristic histologic changes in the bone marrow and the spleen without detectable involvement of even a solitary lymph node. He concluded that the changes in the marrow "may have been primary." It is possible, perhaps even probable, that the initial changes in his case were in the enlarged spleen, because this organ offers richer opportunities than the marrow for the causative agent to produce hyperplasia of lymph follicles. Also, "primary" or predominant Hodgkin's disease of the spleen is a recognized pathologic entity, while changes in the marrow such as Krumbhaar described demand more than ordinarily severe scrutiny before they can be accepted as "primary." In any event Krumbhaar's case serves to emphasize that consideration of changes in the marrow is essential for an intelligent interpretation of the pathology of Hodgkin's disease.

The changes seen in the marrow in Hodgkin's disease suggest an explanation for the alterations in the lymph nodes and in such other organs as may be involved—that the presence of multilobular or multinuclear and mononuclear myeloid giant cells, eosinophils and eosinophilic myelocytes is an indication of disturbances of the marrow resulting in increased expulsion of these cells, which are then deposited in the lymph nodes and other organs. As the disease develops, the hyperplastic lymph follicles disappear, the lymph cords are merged into sheets of lymphoid cells, and cells of at least two alien types make their appearance and lend individuality to the microscopic picture. The cells of one type may be found lying free in varying numbers in the lymph sinuses or among the lymphoid cells. They are large rounded cells resembling the large mononuclear nongranular cells of the normal marrow or hemocytoblasts. The other type is a larger cell which morphologically is identical with that encountered in the normal mammalian marrow in the form of the megakaryocyte. In a later stage these myeloid giant cells may be seen in the tissues of a lymph node, which at this stage has become more or less richly permeated by delicate strands of connective tissue. In the liver, the spleen and other tissues affected by Hodgkin's disease the histologic changes are identical with those in the lymph nodes, or, at all events, there is no essential difference, and the microscopic diagnosis may be made with equal facility.

The megakaryocyte is a large cell, often 35 to 40 microns in diameter. Even in normal circumstances its style of organization is baroque, and the shapes assumed by its degenerate and dying forms are no less arresting.

Its nucleus is rich in chromatin, complex in arrangement and, in man and most other mammals, is deeply constricted and thrown into bulging or overlapping lobules which are connected with one another by short stalks; in other instances it is multinuclear rather than multilobular, particularly in the earlier stages of its development. According to the unitarian school of hematology, the megakaryocyte is a further developmental phase of the hemocytoblast. Minot (1922) found small numbers of megakaryocytes in the blood stream in Hodgkin's disease, and Symmers (1924) observed them lying free and unattached in distended capillary blood vessels in the enlarged lymph nodes of the same disease. In one and the same case of Hodgkin's disease Symmers has demonstrated deformed and degenerate megakaryocytes in sections of the marrow together with identically deformed and degenerate megakaryocytes in the lymph nodes, the spleen and the liver. This seems to be conclusive evidence that they are derived from the marrow by the process of embolism. However, there are informed students who are qualified to challenge the view that the giant cells in Hodgkin's disease are megakaryocytes. Sternberg, Reed, Longcope, McJunkin, Krumbhaar and others believe that the cells in question are derived from endothelium. The contention that they are megakaryocytes apparently finds support only from the observations of Symmers and of Medlar. Symmers regards them as emboli from the marrow, and Medlar interprets them as cells metastasizing from a primary malignant tumor of the marrow or megakaryocytoblastoma. According to Wallhauser (1933):

> . . . The reticulo-endothelial system has been brought into considerable prominence, chiefly by Piney, who repeatedly suggested "that Hodgkin's disease is to be regarded as being essentially a proliferation of reticulo-endothelium and its derivatives," and called it a reticulo-endotheliosis. Rolleston, in commenting on Piney's theory, brought out an interesting point—that if the process were primarily a proliferation of endothelial and reticular cells, "Kupffer's cells in the spleen and liver should be constantly and predominantly affected, and this is not the case."

An obvious fallacy in Rolleston's argument is that the corresponding cells in the lymph nodes and the marrow likewise escape in Hodgkin's disease—that none of the endothelial cells of the reticuloendothelial system participates in the histogenesis of this disease. It follows that the endothelial cells of the reticuloendothelial system may be disregarded in Hodgkin's disease, provided that one may also disregard the view advanced by Reed and others that the multinuclear or multilobular giant cells present in the same disease arise from the endothelium of the sinuses of the lymph nodes.

That the megakaryocytes of the marrow produce blood platelets is generally accepted. In Hodgkin's disease it has been shown that the platelets may increase, their number not uncommonly reaching as high as 750,000 per cubic millimeter (Bunting, Cunningham, McAlpin and

Von Glahn), as opposed to the normal, which is believed to be about 350,000 (Todd and Sanford). Since the platelets are derivatives of megakaryocytes, it is a legitimate inference that an increased number of platelets in the peripheral blood indicates increased activity of the marrow. This interpretation may be invoked also to support the view that hyperactivity of the marrow is an essential factor in bringing about the histologic changes which are characteristic of Hodgkin's disease.

There seems to be no recorded comprehensive studies of film preparations of marrow cells in Hodgkin's disease, all of the comparatively few studies having been made of fixed tissues embedded in paraffin or celloidin (a concentrated pyroxylin), in which cell details are apt to be poorly differentiated. It is true that in the latter preparations the majority of cells may be recognizable as to types—megakaryocytes, eosinophils and eosinophilic myelocytes—but the minute structure of the mononuclear giant cell is not brought out with sufficient clarity to enable one to make even an intelligent guess as to its status—whether it is a normal or an abnormal cell, whether it belongs to the granular or to the nongranular leukocyte series or whether it is an immature megakaryocyte. For convenience sake it may be classified as a hemocytoblast if one is a disciple of the unitarian doctrine, or as either a lymphoblast or a myeloblast if one is of the polyphyletic school, the two last-named cells being morphologically indistinguishable one from the other, so that the developmental potentialities of both are unpredictable —one cannot say which of these two apparently identical cells is to develop into a lymphocyte and which into a myelocyte. The fact remains that in the marrow as well as in the lymph nodes and other tissues in Hodgkin's disease there is a large mononuclear, apparently nongranular cell which corresponds in size and structure to a similar if not identical cell in the normal mammalian marrow.

The polynuclear eosinophil is another cell which forms an important feature of the histologic aspect of Hodgkin's disease. It is found in varying numbers in a large percentage of all cases. The eosinophilic myelocyte, an apparently related cell, occurs likewise in varying numbers, in the lymph nodes, in about a third of all cases. Sometimes it is the only eosinophilic cell present; at other times it is associated with polynuclear eosinophils. The presence of eosinophilic myelocytes in the lymph nodes seems to be a further sign that Hodgkin's disease is attended by disturbances of the marrow, and their presence in the former localities is presumptive evidence that the marrow has not been able to supply eosinophils in adequate numbers and has been forced to disgorge immature and similarly granulated substitutes.

That megakaryocytes occur in the blood and in the lymph nodes, the spleen and the liver in chronic myeloid leukemia is well recognized and is ascribed to embolism originating from the marrow. There seems to be

no reason why the same argument should not be applied to Hodgkin's disease, in which megakaryocytes have been identified in the blood and in the lymph nodes, the liver, the spleen and other tissues, together with eosinophils and eosinophilic myelocytes; in other words, the reaction of the marrow in Hodgkin's disease and in chronic myeloid leukemia is fundamentally the same, although the two diseases differ in the relative number of cells discharged into extramedullary tissues. In myeloid leukemia the marrow is hyperplastic; myelocytes are discharged into the blood stream in large numbers; megakaryocytes are discharged in small numbers and on infrequent occasions, and may be found in the peripheral blood and in the blood vessels of the deeper organs, notably in the sinusoids of the liver and in the spleen and lymph nodes (Bunting, 1911; Minot, 1922). In Hodgkin's disease the marrow is less richly hyperplastic and megakaryocytes are discharged in small numbers at irregular and infrequent intervals. They have been found in the peripheral blood, and that they are not more commonly detected there is probably due to the fact that they circulate in small numbers and at irregular intervals. In the lymph nodes, the spleen, the liver and other tissues they are often the most prominent, although not the predominant, cells in the microscopic picture.

Further evidence tends to show that Hodgkin's disease and chronic myeloid leukemia are more intimately related than is customarily indicated by textbook presentations. Among 36 cases of myeloid leukemia investigated post mortem at Bellevue Hospital (Symmers) there were 8 (22 per cent) in which no lymph node enlargements were observed; lymph node enlargements numbering from two or three to a dozen or more and measuring from 0.5 to 1.5 cm. in their longest diameters were found in 15 (41.6 per cent), and lymph node enlargements numbering from a dozen to an estimated hundred or even more and measuring from 1 to 7 cm. in their longest diameters were found in 13 (36 per cent). In 3 of the 36 cases (8 per cent) the superficial nodes alone were involved; the superficial nodes were involved in combination with the deeper nodes four times (11 per cent), and in 21 cases (58 per cent) there were lymph node enlargements in the thorax or the abdomen or both. The most pronounced case of lymph node enlargements was that of a patient in whom all the superficial groups were involved, the individual nodes measuring from 1 to 7 cm. in their longest diameters; the intrathoracic nodes were discrete and were described as "markedly enlarged," measuring, on an average, 4 cm. in their longest diameters, while the abdominal nodes were "numerous" and likewise enlarged up to 4 cm. in diameter. In a case investigated by necropsy at the Goldwater Memorial Hospital the mesenteric lymph nodes and those around the aorta and both iliac arteries and the pancreas, as well as those in both inguinal regions and around the femoral vessels and in the submaxillary

and supraclavicular regions, were enlarged in great numbers, the individual nodes measuring from 0.5 to 5 cm. in their longest diameters. The nodes were discrete but closely packed. In such cases the enlargement of the lymph nodes is due practically exclusively to infiltration of myeloblasts and myelocytes, but in some of the nodes there is an admixture of megakaryocytes. It is only in the latter circumstance that the resemblance to Hodgkin's disease is apparent.

The lymph node enlargements in fatal cases of myeloid leukemia when compared with those in fatal cases of Hodgkin's disease are few and small, but by no means are they to be regarded as negligible; rather they tend to serve as additional evidence that in myeloid leukemia and in Hodgkin's disease the causative agent brings about changes in the lymph nodes that are qualitatively alike but quantitatively different. In myeloid leukemia the lymph nodes are enlarged partly because of diffuse hyperplasia of lymphoid cells. In this respect they correspond to the smaller and more recently involved lymph nodes in Hodgkin's disease at that stage of development where lymphoid hyperplasia is the predominant feature. There are instances, however, in which the changes in the lymph nodes and the spleen in myeloid leukemia might conceivably be mistaken, histologically, for those of Hodgkin's disease because of the great numbers of mononuclear and multilobular or multinuclear giant cells and of eosinophilic myelocytes among the hyperplastic lymphoid cells. While in Hodgkin's disease, in the majority of cases, enlargement of the lymph nodes is excessive, in some instances it does not greatly transcend that of myeloid leukemia. It appears that in myeloid leukemia and Hodgkin's disease there is a parallelism between the reaction of the bone marrow and that of the lymph nodes and spleen which suggests that the two diseases are different quantitative responses to related causative agents.

Hodgkin's Disease as a Primary Malignant Neoplasm.—At the present moment the view is almost universally entertained that Hodgkin's disease is an infective process. A second view is that the disease is a primary cancer of lymph nodes and that all nodules in other tissues are metastatic. On the other hand, Medlar (1931) expressed the belief that Hodgkin's disease is a primary malignant neoplasm of the bone marrow, from which megakaryocytoblasts are transported through the blood stream to the lymph nodes and other lymphoid tissues. This is reminiscent of the suggestion made by Symmers seven years previously (1924) that Hodgkin's disease is a process of myeloidization of lymphoid structures in which embolism caused by megakaryocytes derived from the marrow plays an essential role. Medlar believes that "the histopathology of Hodgkin's disease is a pleomorphic aggregation of cells which represent the developmental cycle of the megakaryocyte." This means, apparently, that the occurrence in the lymph

nodes of eosinophils and eosinophilic myelocytes is coincidental and that the only constant feature in the histologic makeup of the lesion is the megakaryocyte or some developmental modification thereof and, perhaps, certain degenerate forms such as occur in the marrow in both normal and abnormal conditions. This reasoning appears to be sound, so that the mononuclear giant cell of Hodgkin's disease, for example, could be explained as a young or modified megakaryocyte. If all this is true, there seems to be no reason why Medlar's view should not be accepted, that Hodgkin's disease is primarily a megakaryocytoblastoma. Symmers' contention that Hodgkin's disease is a "toxic" or "inflammatory" disease characterized by myeloidization of lymph tissue, the composite of cells being derived from the marrow by the process of embolism, and Medlar's contention that Hodgkin's disease is a malignant neoplasm of the marrow composed exclusively of cells which represent different phases of the life cycle of the megakaryocyte are, it seems, two ways of arriving at the same conclusion. Whether either of these claims is valid will no doubt be revealed when it is divulged just where inflammation ends and neoplasia begins. During the interim this particular question will doubtless find a place in academic discussions of the nature of Hodgkin's disease.

Assuming for argument's sake that Hodgkin's disease is not primarily a malignant tumor, the question arises whether it is capable of cancerous transformation. That it may be locally cancerous cannot be denied—it possesses qualities which may bring about mechanical injury to, or invasion and destruction of, tissues. Apparently, it has never been shown to metastasize, which, after all, is the best qualification for the determination of malignancy; that is to say, it has never been shown in Hodgkin's disease that a given lesion was producing a single type of cell, say, the large mononuclear cell, in such numbers as not only to dominate the picture locally but to travel by the blood or the lymph stream to distant lymphoid or other tissues and set up independent new growths possessing a histologic character different from that of the parent cell complex from which it was derived. It seems that the term "Hodgkin's sarcoma" should be abandoned.

PATHOLOGIC ASPECTS

Hodgkin's disease is a pathologic entity. According to one view (Symmers, 1924), the cases may be divided into two groups. In the first group are those cases in which the changes are limited to the lymphoid structures, that is, to the lymph nodes and the spleen, and the various auxiliary lymphoid depots, including those in the walls of blood vessels, especially the larger veins, in the lungs, the bone marrow, the kidneys, the adrenal glands, the subcutaneous tissues, the serous membranes and elsewhere. The second group includes those cases

in which, in addition to involvement of the various lymphoid structures, the growths mechanically infiltrate muscles, including the heart, and by direct pressure erode bone or partially replace viscera. According to another view (Jackson and Parker, 1944), there are three types of Hodgkin's disease, namely, Hodgkin's paragranuloma, a relatively benign form, which may develop into Hodgkin's granuloma, a disease of intermediate severity, which, in turn, may undergo sarcomatous transformation.

Lymph Nodes.—The term "primary Hodgkin's disease" is often used to indicate the greatest degrees of enlargement of the lymphoid structures encountered anatomically and representing, presumably, the oldest lesions. The term is to be avoided because it is apt to convey a false conception of Hodgkin's disease, which has multiple foci of origin, occurring at the same or approximately the same time in the lymph nodes of the same or of separate groups, and because the nodes of one group may enlarge progressively while those of another group may recede or remain stationary, at least for a while. Nevertheless, it is often practicable to arrive at a reasonably safe conclusion as to the comparative age of the respective enlargements, whether of the lymph nodes proper or of such lymphoid organs as the spleen and the thymus, and thus to provide a classification of working value.

As far as Hodgkin's disease is concerned, the lymphoid structures of the body may be divided into three groups:

(*a*) In the first group are the nodes of the neck, the axillas, the thorax, the abdomen and the groins. These are the nodes which carry the great share of the burden of Hodgkin's disease.

(*b*) In the second group are the submucosal collections, represented by the faucial and lingual tonsils and by the lymphoid follicles which are strewn through the submucosa of the gastrointestinal, respiratory and urinary tracts. They are accumulations of lymphoid cells, the aggregate of which is probably equal to, if not greater than, the sum total of the regional collections of group *a*. These submucosal lymphoid structures almost invariably escape in Hodgkin's disease.

(*c*) In normal circumstances the auxiliary lymphoid system is represented by follicles in the walls of the arterioles of the spleen. Beyond the spleen, and with the possible exception of the lymphoid cells of the thymus, the auxiliary lymphoid system is negligible in normal circumstances, but in certain pathologic conditions it assumes importance. Thus, in Hodgkin's disease focal collections of lymphoid cells are to be found in the walls of the perilobular portal veins. They represent hyperplasia of preexisting lymphoid collections, which are anatomically comparable to the follicles of the spleen. In Hodgkin's disease, also, the interstitial tissues of the kidney occasionally show focal collections of

lymphoid cells, usually in the richly vascularized cortex, in proximity to, but not in the walls of, the blood vessels. Similar foci occur in the cortex of the kidney in enteric fever, perncious anemia, lymphosarcomatosis and pseudoleukemia. In the interstitium of the lungs or in the walls of blood vessels, collections of lymphoid cells may be seen in various pathologic conditions, and the same statement applies to the serous membranes and to the subcutaneous tissues, the bone marrow, the interstitial tissues of the prostate, the adrenal gland, the thyroid gland and elsewhere. In Hodgkin's disease, the initial changes in the auxiliary lymphoid tissues are comparable to those in the lymph nodes, and their subsequent development is the same, although oftenest on a miniature scale.

Preponderant Cervical Hodgkin's Disease.—It seems to be a sort of tradition that Hodgkin's disease is a primary or a preponderant disease of the cervical lymph nodes. This conception, however honored by repetition, is contradicted by fact. Reed states that the disease "almost always begins in the cervical region" and that "we know of no case where the pathological anatomy was described in sufficient detail to permit of a positive diagnosis, in which the disease commenced elsewhere." She based this conclusion on 8 cases, in 3 of which necropsy was performed. Longcope based a like opinion on a study of 8 cases, in 3 of which necropsy was performed. At Bellevue Hospital, in 30 cases investigated by necropsy, preponderant enlargement of the cervical nodes was encountered once only (3 per cent). In 10 of the 30 cases (33 per cent) the predominant enlargements occurred in the abdominal lymph nodes, while in 9 cases (30 per cent) the lymph nodes of the chest and those of the abdomen were predominantly enlarged in company with one another. In other words, predominant Hodgkin's disease of the abdominal lymph nodes or of the combined abdominal and thoracic nodes occurred in 63 per cent of 30 cases submitted to postmortem examination—a ratio of 19 to 1.6. In 7 of the 30 cases the superficial nodes were not involved at all (23 per cent); in 13 they were involved to a slight extent (43 per cent), and in the remaining 10 cases (33 per cent) they were moderately or markedly enlarged in association with collections in the deeper parts that were of far more massive proportions. In many quarters Hodgkin's disease is now accepted as oftenest a primary or a preponderant disease of the lymph nodes of the abdomen or of the abdominal and thoracic nodes combined. From necropsy experience it appears that the changes in the deeper lymph nodes are "primary," that they may remain apparently dormant for months or even years, giving rise to no symptoms or signs, and that, if enlargement of the superficial nodes occurs at all, it is a late warning and indicates that the disease has gained widespread pro-

portions in the abdomen or the thorax or both. Moreover, it is a subject of clinical value—not necessarily a matter of anatomic sequence—that enlargement of the axillary nodes is suggestive of predominant involvement of the thoracic groups, and that inguinal adenopathy is suggestive of predominant involvement of the abdominal nodes. Enlargement of the axillary or inguinal nodes independent of such associations, if it exists, was not recognized in the Bellevue Hospital series.

The manner in which the lesions are distributed in the lymph nodes of the thorax and the abdomen seems to warrant the view that the causative agent of Hodgkin's disease enters the body through mucous membranes, perhaps most often through the mucous membrane of the intestinal tract, and that it produces its greatest degree of reaction in those lymphoid structures which are situated at strategic points for purposes of filtration, more especially in the lymph nodes of the thorax and the abdomen.

Enlargement of the superficial lymph nodes, in Hodgkin's disease, when it occurs at all, may show itself first in the lower part of the neck just above the clavicle, oftenest, according to some observers, on the right side. According to other observers, the order of appearance does not follow any rule. The skin covering the enlarged nodes is intact and unattached. The nodes are discrete and separated from one another by filmlike partitions of connective tissue. They vary in size from a few millimeters to several centimeters, and when not too closely packed, are rounded or ovoid. When closely packed they show the effects of reciprocal pressure or of the pressure which they themselves exert against the surrounding structures. In such circumstances their shape is altered, the nodes becoming flattened or otherwise distorted, although the dividing lines between them still are discernible, and fusion seldom occurs. Their consistence varies, depending on the amount of connective tissue in them. In the earlier stages they are soft and rather elastic. As the connective tissue increases in quantity, the nodes become correspondingly firmer and tend to lose their resiliency. In the later stages individual nodes or several nodes of the same or of different groups may undergo fibrous replacement to such an extent as to convey a stonelike sensation to the palpating finger. In such nodes the connective tissue not infrequently is hyalinized, either in patches or diffusely, and the histology is so obscured that in any given microscopic field recognition of the disease is difficult or impossible. Such changes are perhaps best interpreted as efforts in the direction of spontaneous healing (Symmers, 1911).

On occasions the appearance of the lesions of the lymph nodes departs from the orthodox forms in such fashion as might lead one astray. In a patient at Bellevue Hospital there was a mass of lymph nodes just below the angle of the jaw on the left side. The mass measured about

7 cm. in diameter at its base. It was adherent to the skin and to the adjacent structures. The skin covering the mass was ulcerated over an area measuring 3 by 1.5 cm., and the enlarged nodes of which the mass was composed were matted together. Thin yellowish pus exuded from the ulcerated surface. In other words, the growth bore a resemblance to the later stages of tuberculous lymphadenitis. However, tissue excised from the mass and examined microscopically showed the histologic aspects of Hodgkin's disease.

When sectioned in the fresh state the nodes more lately involved in Hodgkin's disease present a smooth and glistening appearance and a grayish or whitish color or, at times, a yellowish tint. The substance may bulge slightly beyond the cut edge of the capsule. It is noticeably free from any indications of even a relatively rich vascular supply. In this respect it differs from the substance of the nodes in lymphosarcoma and lymphoid leukemia, which often show reddish dots or streaks or even hemorrhagic splotches. In rare cases of Hodgkin's disease, minute elevations, rounded and circumscribed, may be detected by the unaided eye or by the use of a hand lens. On microscopic examination they are found to represent hyperplastic lymph follicles.

Spleen.—Enlargement of the spleen is oftenest second in order of appearance to enlargement of the lymph nodes but in occasional instances the burden of the disease is borne by the spleen, almost alone. For example:

> In 1909 Symmers described the case of a girl 18 years of age who, for a period of three years before admission to the New York Hospital, knew that there was a mass in the left side of her abdomen. The superficial lymph nodes were not enlarged. The edge of the spleen was felt just above the inguinal ligament on the left side, whence it could be traced to the right as far as the umbilicus and thence upward. The organ was removed at operation and measured 25 by 18 by 8 cm., and on microscopic examination, presented the histology of Hodgkin's disease. At the time of operation no enlarged lymph nodes were seen or felt in the abdomen. Death occurred, but permission to do a necropsy was not obtainable. Since then Symmers has encountered at necropsy a series of 6 additional cases at Bellevue Hospital in which the spleen was massively increased in size, weighing on an average 1,136 or 936 Gm. above the high normal weight of the spleen of the adult. There was associated enlargement of a few lymph nodes, usually in the abdomen, but occasionally in the neck. The number of the enlarged lymph nodes and their size, however, were insignificant as compared with the extent to which the spleen was enlarged.

Similar examples, likewise verified at necropsy, have been recorded by Cornwall and by l'Esperance.

Cases of the sort described indicate the existence of a variety of Hodgkin's disease in which the spleen is "primarily" involved. There can be no question that in certain cases there is a phase in the clinical evolution of Hodgkin's disease that is marked by enlargement of the

spleen before recognizable signs of involvement of the lymph nodes of the chest, the neck or the abdomen appear. For example, at Bellevue Hospital there was a patient whose spleen reached into the pelvis and as far forward as the mamillary line. She was under observation for several weeks, with the enlarged spleen as the only clinically detectable sign of disease. Finally, a small, barely palpable lymph node appeared in one of the anterior cervical triangles. The node was removed, and microscopic examination showed the histologic changes of Hodgkin's disease. All of these facts appear to confirm the opinion that there is a variety of Hodgkin's disease in which the preponderant lesions are in the spleen, while changes occurring in the lymph nodes are trivial in both extent and number.

Of the 30 cases in the Bellevue Hospital series, the spleen was apparently secondarily enlarged in 20, or in 66 per cent, and in all of them the organ was nodular. The individual nodules were more or less sharply defined and somewhat elevated, and measured from a few millimeters to several centimeters in diameter. The background color varied from deep red to pink, depending on the content of blood in the red pulp, and, standing out in contrast, were patches or streaks of grayish translucent tissue representing, histologically, foci of growth not to be distinguished from those in the diseased lymph nodes. In some instances the spleen shows areas of necrosis. Sometimes necrosis reaches marked proportions and may be associated clinically with the Murchison syndrome or, as it is more familiarly and less deservedly known, the Pel-Ebstein syndrome.

In the Bellevue Hospital cases the average weight of the spleen was 801 or 601 Gm. in excess of the high normal weight of the spleen of the adult in health. In all of the 20 cases of splenomegaly characteristic histologic changes were present. In 4 other cases the histologic changes observed in the spleen were those of Hodgkin's disease, but the organ was normal in size or only slightly enlarged and could not be palpated during life. In another 4 cases the spleen was normal, both in size and microscopically. In short, in one third of the 30 cases of Hodgkin's disease investigated by necropsy at Bellevue Hospital the spleen could not be felt during life.

Thymus.—That the thymus participates in Hodgkin's disease has been generally recognized only within comparatively recent years. In 1904 Yamasaki recorded the case of a 32 year old woman who at necropsy presented a mass in the superior part of the mediastinum simulating the shape of the thymus. It covered the precordium and penetrated the parietal pericardium at several points. The growth invaded the pleura of the right lung and compressed the substance of the lung itself. The sternum was eroded, and the walls of the left innominate vein and of the superior vena cava were infiltrated. In the neck and in the

region of the stomach the lymph nodes were slightly enlarged. Seven additional cases of primary or preponderant Hodgkin's disease of the thymus have been recorded by Chiari, Lyon and Symmers. In 7 of the 8 cases enlargement of the lymph nodes or of the spleen, if present at all, was of slight or of moderate proportions. In the remaining case the retroperitoneal nodes were described as "numerous and greatly enlarged."

Liver.—As Hodgkin's disease is portrayed in various texts, involvement of the liver, if mentioned at all, is usually dismissed in a few words, and the anatomic changes and their clinical significance are seldom, if ever, discussed. In actual experience the liver participates in Hodgkin's disease with about the same frequency as the spleen. The liver may be so affected as to cause signs of obstruction, such as jaundice or ascites, leading to the suspicion of Laennec's cirrhosis or of hepar lobatum.

In 17 cases of the Bellevue Hospital series (58 per cent) the liver presented foci of characteristic histologic structure, which varied in size from 0.5 to 2 cm. Microscopic examination showed that the disturbance arose in the periportal spaces and was evidenced initially by hyperplasia of lymphoid cells in the walls of the portal veins, subsequent to which mononuclear and multilobular or multinuclear giant cells appeared among the lymphocytes, with or without the presence of eosinophils and eosinophilic myelocytes, the whole supported in a connective tissue reticulum. The nodules thus formed expanded in such fashion as to subject the neighboring lobules to pressure, with resultant atrophy.

In one of the 3 Bellevue Hospital cases of primary or preponderant Hodgkin's disease of the liver, the patient, a woman aged 40 years, complained of enlargement of the abdomen that had been progressing for a period of three months. The skin was tinged slightly yellow. The abdomen was prominent, and there were signs of a fluid wave and of shifting dulness. The lower edge of the liver was palpated at the level of the umbilicus. The spleen was not felt. After paracentesis and the removal of 4,400 cc. of clear yellow fluid, the edge of the spleen was palpated in the anterior axillary line. At necropsy the abdomen contained about 500 cc. of clear fluid. The liver was enlarged, the lower margin lying at the level of the umbilicus. Its shape was normal. The surface was smooth except for a number of minute whitish nodules, the largest of which were about 5 mm. in diameter. The parenchyma was permeated by large bands of fibrous tissue, smooth and opaque, which followed the distribution of the portal system. At the time of necropsy it was estimated that two thirds of the liver was thus replaced. On cross section the fibrous bands were rounded, often approximating the size of one's little finger; they were distinctly differentiated from the remnants of liver tissue and frequently presented at the center a

minute dimple, corresponding to the cut end of a blood vessel. In other places were similarly rounded masses which were only a few millimeters in diameter. Between these and the larger ones were fibrous areas of different gradations in size. The liver tissue in the immediate vicinity presented signs of compression, the lobular remnants being small and irregular in shape. The mesenteric and retroperitoneal lymph nodes were moderately increased in number and varied in size from 1 to 3 cm. No other enlarged lymph nodes were encountered. The spleen was normal in size.

Bone.—In a series of 14 cases of Hodgkin's disease encountered at necropsy at Bellevue Hospital, the bone marrow was involved in 7, or 50 per cent. This corresponds to Turnbull's experience at the London Hospital, where involvement of the marrow was encountered in 19 of 39 cases, or 49 per cent. In one of the Bellevue Hospital cases the marrow of all the thoracic and lumbar vertebrae was completely replaced by tissues of the same sort as that in the lymph nodes, the intervertebral disks and the bony casements of the vertebral bodies remaining intact. In another case the anatomic diagnosis referred to "extensive replacement of the vertebrae," but the text of the protocol made no mention of the part of the vertebral column involved. In the remaining 5 cases the marrow spaces were occupied to a variable extent by tissue microscopically identical with that of the diseased lymph nodes.

Muscle Tissues.—In one of the cases of Hodgkin's disease investigated by necropsy at Bellevue Hospital the enlargement of thoracic lymph nodes was attended by penetration of the intercostal muscles and infiltration of the muscles of the corresponding pectoral region, producing a mass which in size and shape resembled a small ham. In a second case the enlargement of cervical lymph nodes was continuous with infiltration of the pectoral muscles on the right side covering an area only slightly smaller than that of an average adult hand, while the enlargement of the abdominal nodes was accompanied by almost complete destruction of the right psoas magnus muscle. In a third case the nodules occurring in the right forearm were attended by continuate infiltration of adjacent muscles and tendon sheaths. In 2 other cases of the Bellevue Hospital series the pericardium was penetrated and the heart muscle invaded. In another case the right auricle was partially replaced; in still another case both auricles and the upper third of the right ventricle were extensively involved by diffuse or nodular deposits. Since 1912 a total of 7 cases of invasion and destruction of the uterine muscle has been recorded (Naumann, 1947).

Blood.—Cunningham (1915) emphasized the variability of the blood in connection with Hodgkin's disease and its lack of diagnostic significance. He agreed with Fabian that "the blood picture changes in one-

fifth of an observation." Cunningham's findings in 10 cases of Hodgkin's disease after repeated examinations of the blood showed variations in the hemoglobin content of from 40 to 110 per cent and in the red cells from 3,000,000 to normal. The total leukocyte count varied from 11,000 to 74,000; polymorphonuclear neutrophils from 68 to 92 per cent; small lymphocytes from 3 to 23 per cent; large lymphocytes from 3 to 5 per cent; transitional cells from 3 to 12.6 per cent; eosinophils up to 2.3 per cent. Occasionally a basophil was present. He stated that the transitional cells are "in general increased," the highest percentage being 12.6 and the average 6.6 To Cunningham's observations are to be added those of several others to the effect that the eosinophil count may sometimes increase to the extent of from 4 to 60 per cent of the total number of leukocytes in the peripheral circulation. Anemia of the myelophthistic or myelofibrotic type may occur in cases of Hodgkin's disease in which the hemopoietic bone marrow is extensively sclerotic (Heller and Sanes, 1947).

Pleurae and Lungs.—Instances of Hodgkin's disease involving the pleura have been recorded by McAlpin and Von Glahn, Yates and Bunting, Symmers and others. In a noteworthy percentage of all such cases exudates collect in the pleural cavities or there is hydrothorax. In one of the Bellevue Hospital cases the parietal and visceral layers were fused, and the entire lung was covered by pleura thickened to the extent of a centimeter. Preponderant or primary Hodgkin's disease of the lung seems not to have been described. Nodular lesions are sometimes found in the pulmonary parenchyma, usually in association with Hodgkin's disease of the thymus or of the thoracic lymph nodes; they arise, most likely, on the basis of preexisting interstitial lymphoid foci. In other cases the disease "extends for varying distances into the lungs as white radiating bands following the interlobular lymphatics" (Simonds, 1926). In still other cases of Hodgkin's disease intrathoracic enlargements compress and partially or completely destroy one or more lobes of the lung with or without invasion of the walls of the trachea and larger bronchi and obstruction or occlusion of their lumens.

Gastrointestinal Tract.—Numbers of cases are recorded as examples of "primary" Hodgkin's disease of the gastrointestinal tract. In most of them the diagnosis was based on tissues which had been removed at operation in circumstances that made it impossible to determine whether lesions of the same character were present in other parts of the body. In some instances microscopic examination of excised tissues showed superficially ulcerated granulomatous lesions in which giant cells were arranged around foreign particles in such fashion as to simulate the histologic picture of Hodgkin's disease or even that of tuberculosis. This form of granuloma occurs in the so-called regional ileitis, in which it causes thickening of the intestinal wall, due to overgrowth of connec-

tive tissue, in which there are focal or diffusely distributed collections of lymphocytes, sometimes eosinophils, and variable numbers of multinuclear foreign body giant cells, some of which may resemble megakaryocytes. In some of these cases, abscesses occur in the wall of the intestine, or the lymph nodes in the vicinity of the ileocecal junction undergo enlargement due to edema, congestion and abscess formation or, in the less acute cases, to numerical and dimensional hyperplasia of the lymph follicles. Clinically, these changes sometimes resemble acute appendicitis; at other times they have been mistaken for tuberculous ileitis.

In a good many instances ulcerative lesions of the pyloric end of the stomach have been recorded under the caption of "primary" Hodgkin's disease. Here the objection again presents itself not only that examination was necessarily limited to the field of operation and that remote lesions in other parts could not be excluded but that convincing histologic evidence was not adduced. In a case recorded by Singer it was shown at necropsy and by subsequent microscopic examination that a large growth of the pyloric end of the stomach was an example of preponderant Hodgkin's disease. The illustrations which accompany Singer's paper are convincing, and the microscopic changes could scarcely be mistaken for those of any other disease. The rarity of Hodgkin's disease of the gastrointestinal tract is further indicated by the fact that in the five largest municipal hospitals in the city of New York not a single example was found among 173 necropsies of patients with Hodgkin's disease.

Skin.—In a certain percentage of all cases Hodgkin's disease is attended by alterations of the skin—among them, such incidental changes as macules, prurigo-like eruptions and lichenification. Some observers lay stress on the so-called café au lait discoloration of the skin, a diffuse, light brownish effect. It occurs in many patients with Hodgkin's disease, particularly in the later stages, but it is also to be seen in chronic lymphoid leukemia and in subacute bacterial endocarditis when a slowly progressive secondary anemia indicates the approach of death.

In 3 of the Bellevue Hospital cases of Hodgkin's disease the skin was the seat of chronic diffuse exfoliative dermatitis, which occurs in association with other forms of lymph node enlargement, such as tuberculous lymphadenopathies and giant follicular lymphadenopathy, indicating a relationship between this type of skin disorder and diseases of the lymph node system.

In still other cases of Hodgkin's disease the skin is the seat of diffuse or patchy pigmentary disturbances. One of the Bellevue Hospital cases may be cited:

The patient presented brownish pigmentation of the skin associated with deep brownish or brownish black macules. The pigmentation involved the skin of the

neck, the chest, the abdomen and the upper portion of the face. The mucous membranes were natural. The blood pressure was low, and the heart sounds were muffled. At necropsy, and microscopically, the adrenal glands were intact. The celiac ganglions, however, could not be identified and were probably submerged in the mass of enlarged lymph nodes that almost completely filled the belly cavity. The changes in the skin bore a resemblance to those encountered in the adult variety of acanthosis nigricans—a condition described independently by Pollitzer and Janovsky in 1891.

Nervous System.—Symptoms and signs referable to the nervous system occur in Hodgkin's disease in a considerable number of cases. Most of them are traceable to the effects of pressure and vary within wide limits according to the distribution of the growths. Common among the neurologic manifestations are signs of pressure due to enlargement of the axillary lymph nodes and involvement of the brachial plexus. In many instances paraplegia has been observed following erosion of bone due to the advancing growths and subsequent pressure on the spinal cord. Herpes zoster sometimes occurs and is a troublesome symptom. It is probably due to compression of the posterior nerve roots and ganglions. Involvement of the parenchyma of the brain or spinal cord occurs but is extremely rare.

SYMPTOMS AND SIGNS

The symptoms and signs of Hodgkin's disease may be divided into several groups:

(*a*) In most instances the patient complains of no subjective symptoms. Occasionally, generalized pruritis is persistent and may accompany the enlargement of lymph nodes or precede its appearance by many months. This symptom is always to be regarded with thoughtful suspicion, although it may also occur in lymphoid leukemia and in the lymphosarcomatous variety of mycosis fungoides.

(*b*) In the majority of cases, the patients seek advice because of palpable or visible enlargements in the neck, the axilla or the groin, or because of signs of increased pressure due to enlarged lymph nodes within the thorax or the abdomen, or to such conditions as predominant Hodgkin's disease of the spleen or of the liver. Enlargement of the superficial nodes is usually a matter of objective concern, since they are painless, but sometimes attention is first directed to them because of pressure effects, such as numbness and tingling of the fingers or the toes due to edema or cyanosis of the corresponding extremity, or jaundice, sometimes intermittent, caused by enlarged lymph nodes pressing on the common bile duct in the vicinity of the hilus of the liver. Other indications of pressure occurring in connection with growths in the abdomen or the thorax consist of symptoms and signs varying in severity from an annoying cough to the terrifying effects of

orthopnea, difficulty of swallowing, paraplegia secondary to deposits in the dura of the cord, or to the consequence of transudations into the pericardium, the pleura or the peritoneum.

(*c*) There is a group of patients in whom subjective symptoms are absent and pressure effects are delayed—the patients complain of no sensations of discomfort for a period of many months or even for years. Suddenly, pressure effects assert themselves, at first intermittently, and then progress rapidly and without abatement, death occurring in a few weeks or months.

Fever.—In about one half of all cases of Hodgkin's disease the temperature is normal. In those cases in which deviations occur, there is nothing in the duration or the extent of the disease to account for them, and some interposing factor must be invoked. A feature in many of the temperature charts is that of irregularity of the wave. In others, all of the classic curves may be simulated—those of tuberculosis, typhoid fever or sepsis (Cunningham, 1915).

The Murchison Syndrome.—There is a small but important group of cases in which the temperature pursues a remarkable course, although the syndrome is not confined to Hodgkin's disease, namely, fever of from ten to fourteen days' duration, characterized by gradual ascent of the temperature to 103 or 104 F. (39.4 to 40 C.), where it is maintained for a period of three or four days, after which it gradually descends and is followed by an afebrile interval of from ten days to two weeks or longer. Similar reactions occur with almost mathematical regularity throughout the patient's illness, which may occupy a term of from six months to a year or more.

The so-called Pel-Ebstein syndrome has given rise to much confusion, partly because the designation is a misnomer and partly because the syndrome is so commonly regarded as a remittent febrile disturbance which occurs in Hodgkin's disease exclusively. It is a misnomer because the syndrome was first described in 1870 by Charles Murchison, of London, England, and not by Pel, of Amsterdam, Netherlands, and Ebstein, of Göttingen, Germany, although the two latter observers, in 1887, or seventeen years later, contributed papers on the same subject independently of one another. The syndrome is not peculiar to patients with Hodgkin's disease but may be observed in patients with certain forms of pulmonary tuberculosis and in patients with hypernephroma and those with perithelial sarcoma tumors, both of which are frequently necrotic. Its occurrence in a diversity of diseases in which necrosis is a frequent factor suggests that it depends, at least in some instances, on secondary infection of necrotic tissues.

Murchison's original case was published seventy-seven years ago in the *Transactions of the Pathological Society of London* under the heading of "A Case of 'Lymphadenoma' of the Lymphatic System,

Spleen, Liver, Lungs, Heart, Diaphragm, Dura Mater," etc. The histologic examinations were carried out by Burden Sanderson. Neither Murchison nor Sanderson seemed to be any too sure that the disease was an example of Hodgkin's "lymphadenoma." This uncertainty is shown not only in the title of Murchison's paper, where the word "lymphadenoma" is in quotation marks, but also in the text, where he refers several times to the resemblance of the disease to "cancer." In addition, Sanderson's woodcut depicting the histologic aspect of the disease, does not bear the slightest resemblance to the histologic aspect of Hodgkin's disease as this is now known. It does, however, show features which are strangely like those of the malignant tumor which is familiar to pathologists under the name of "perithelioma" or "perithelial sarcoma." In any event it would seem fair to designate the remittent febrile disturbances with which the several diseases mentioned are sometimes accompanied as Murchison's syndrome rather than as the Pel-Ebstein syndrome or disease.

DIAGNOSIS

Making a clinical diagnosis of Hodgkin's disease on the basis of its symptoms and signs is an interesting if precarious venture. If it is attempted and if subsequent investigation shows that the attempt was successful, the result is to be ascribed to fortuitous guesswork rather than to excellence in the art of diagnosis. There are at least six other conditions in which the symptoms and signs may be almost identical, although among them minor clinical differences may occur in favor of the diagnosis of one disease as opposed to the others, but these differences are few, inconstant and subject to variations among themselves.

Gordon's test (1933) is of some value in the diagnosis of Hodgkin's disease and in the exclusion of certain other diseases of the lymphoid system. Fresh lymph nodes are minced under sterile conditions and suspended in nutrient broth; after seven days' incubation a small amount of the supernatant broth (0.5 cc.) is injected intracerebrally in rabbits or guinea pigs. A positive reaction appears in from two to five days. It consists of such signs as spastic paralysis, muscular weakness, tremors, opisthotonos and nystagmus. Microscopic examination of the cerebellum shows loss of the cells of Purkinje. According to Steiner (1941), of 331 tests carried out by 23 workers, the test was positive in slightly over 74 per cent. In the 40 control cases (lymphosarcoma, pseudoleukemia, lymphoid, myeloid and monocytic leukemia, nonspecific and tuberculous lymphadenitis) the test was negative. Thus far it appears not to have been applied in cases of giant follicular lymphadenopathy, in which it is conceivable that it might be of diagnostic value. The test is not specific since there may be similar reactions with normal spleen or bone marrow.

Commenting on Gordon's test Krumbhaar says:

> . . . If the opinion is substantiated that this procedure has diagnostic value, it will not only be a great relief to have a biologic as well as a morphologic attack on biopsy material, but it also should advance our understanding of the disease and perhaps place it definitely in the group of virus diseases. With the known prevalence of latent virus diseases in laboratory animals, however, and their activation by non-specific agents, attribution to this virus of a causative role in Hodgkin's disease must be made with utmost caution.

There is but one procedure which insures accuracy of diagnosis—the removal of an enlarged lymph node and examination to determine in it those histologic changes which characterize the disease. Otherwise, Hodgkin's disease might readily be confused with giant follicular lymphadenopathy, lymphosarcoma, chronic lymphoid leukemia, generalized tuberculosis or syphilis of the lymph nodes, and the metastatic spread of cancers through one or several of the peripheral groups of nodes. Removal of tissue for diagnosis is a justifiable procedure, although it should be carried out with the precautions customarily observed in surgical operations. The groin should be avoided because infection is more apt to occur in this region and be troublesome, sometimes fatal, as in a case in the Bellevue Hospital series. Spread of the disease following diagnostic removal of tissue, if it ever occurs, is to be regarded as a coincidence. The objection that this procedure may be followed by rapid dissemination is gratuitous and is based on the assumption that cells are liberated by operative manipulation and transplanted to remote parts.

DURATION

The rarity of subjective symptoms of Hodgkin's disease is of itself an interesting revelation, but the degree to which enlarged lymph nodes may exist in the abdomen or the thorax or both without causing symptoms or signs of any sort until after the lapse of many months is an illustration of the degree to which the thoracic and abdominal viscera may adapt to the effects of gradually increasing pressure. Because of this fact it is impossible intelligently to estimate the duration of the disease. After superficial lymph nodes have enlarged and the diagnosis has been established by an examination of tissue submitted for biopsy the patient's life expectancy can only be guessed. It probably lies somewhere between two and five years. In 1 of Cunningham's cases the patient, who had not been treated, was known to have had Hodgkin's disease for a period of twenty-five years.

TREATMENT

No method of treatment thus far devised has been shown to influence the disease favorably for more than a short time, and even in such circumstances it may be difficult to judge the effects of treatment

because of the proclivity of the enlarged nodes to regress spontaneously and after intercurrent infections or, without apparent reason, to remain stationary for an indefinite period. Surgical intervention is useless and should never be undertaken except for mechanical relief of conditions which threaten life or are intolerable.

In recent years, nitrogen mustards have been used in the treatment of Hodgkin's disease. Whether the effect is more prolonged or more complete than that produced by roentgen rays remains to be determined (Gilman and Phillips, 1946; editorial, *The Journal of the American Medical Association,* 1946). The use of radioactive phosphorus "has not proved of therapeutic value" in Hodgkin's disease (Hoster and Doan, 1945).

The roentgen ray treatment of Hodgkin's disease is sometimes followed by remarkable diminution of the diseased nodes, but no instance of cure obtained by this means seems thus far to have been recorded. There appears to be no acceptable explanation of the changes observed in the lymph nodes after roentgen therapy. It has been claimed that the apparently favorable effects are due to vascular occlusion followed by death of the cells and their replacement by connective tissue. In a case of Hodgkin's disease recorded by McAlpin and Von Glahn, the patient had received ninety-five roentgen ray exposures. Lymph nodes were removed and submitted to microscopic examination before the administration of radiation therapy and after the death of the patient. According to the microscopic descriptions and from the illustrations which accompany their paper, the nodes, in both instances, showed no changes which could be reasonably ascribed to any specific action of the roentgen rays, all of the changes being a counterpart of those encountered in lymph nodes that had not been submitted to radiation. It remains to be decided whether reparative alterations are to be accredited to man's therapeutic ingenuity or to some beneficent provision that nature makes for tissues in distress.

GIANT FOLLICULAR LYMPHADENOPATHY

Giant follicular lymphadenopathy is a comparatively newly identified disease of the lymhp nodes and the spleen. It was described by Becker, in 1901, apparently for the first time. He could not classify it other than in the indeterminate category of pseudoleukemia, which in Germany at that time was used to include almost every form of otherwise unexplainable enlargement of lymph nodes and spleen. In 1925 Brill, Baehr and Rosenthal, and in 1927 and again in 1938 and 1942 Symmers, called attention to a disease without specific changes in the blood characterized anatomically by generalized or regional lymphadenopathy with or without splenomegaly. They emphasized its clinical importance and the fact that it was amenable to radiation therapy. Symmers observed that giant follicular lymphadenopathy is almost always mistaken clin-

ically for Hodgkin's disease, less often for lymphosarcoma, chronic lymphoid leukemia and other diseases marked by progressive enlargement of the lymph nodes. He also emphasized that the histologic appearance of the lymph nodes in giant follicular lymphadenopathy is distinctive and that on histologic grounds alone differentiation may often be made almost at a glance.

Becker's case was that of a woman aged 33 whose illness appeared to commence with swelling of the lymph nodes of the neck, followed in the course of the next three years by enlargement of all the superficial lymph nodes, some of which reached "the size of a walnut." The spleen was massively enlarged. The red cell count was 4,500,000; the hemoglobin content, 70 per cent. The white cell count was 9,400, with 44 per cent polymorphonuclear neutrophils, 51 per cent lymphocytes, 3 per cent eosinophils, 0.8 per cent mononuclear and transitional cells and 0.3 per cent mast cells. A solitary lymph node removed three years after the onset of illness showed the histologic signs of "simple hyperplasia." "Simple hyperplasia" may be assumed to mean "hyperplasia of "lymph follicles," although it could be equally well construed as diffuse hyperplasia of lymphocytes following the disappearance of hyperplastic follicles, such as occurs in chronic lymphoid leukemia. The combined features of the disease seem to make it practically certain that Becker's case was one of giant follicular lymphadenopathy, although the fairly high lymphocyte count suggests that it might have been one of lymphoid leukemia.

However this may be, Brill, Baehr and Rosenthal, in 1925, described 2 cases about the nature of which there is no cause for doubt:

The first case was that of a woman aged 28 who presented generalized enlargement of the superficial lymph nodes, the nodes varying in size from that of "a pea to that of a walnut"; the nodes were movable and free from tenderness. The spleen reached from the level of the eighth rib on the left side to the anterior-superior iliac spine and to the right for a distance of 5 cm. beyond the midline. Microscopic examination of lymph nodes excised from the neck and the axilla "failed to show any evidence of Hodgkin's disease, lymphosarcoma or tuberculosis." The changes were confined to enlargement of the lymph follicles. Under roentgen therapy the splenic and lymph node enlargements disappeared.

The second case was that of a woman aged 32 who complained of gradual enlargement of the abdomen of two months' duration. The spleen extended from the eighth intercostal space above to the brim of the pelvis below and within 2 cm. of the midline. The cervical, axillary and inguinal nodes were moderately enlarged. Microscopic examination of the spleen and of an enlarged lymph node removed from the abdomen showed hyperplasia of the lymph follicles in both. Later, the axillary nodes became enlarged but disappeared under roentgen therapy.

In 1927 Symmers published 3 cases of the same character:

The first was that of a man aged 32 who, in 1921, presented moderate generalized superficial lymphadenopathy with splenomegaly. Nine years later he died of Hodgkin's disease.

The second case was that of a girl aged 7 who was admitted to Bellevue Hospital because of enlarged superficial lymph nodes which had been present for two and one-half years. The spleen was palpable two thirds of the distance from the xiphoid process to the umbilicus. Enlarged lymph nodes were removed from the inguinal and cervical regions, and on microscopic examination no alteration was found in them other than numerical and dimensional hyperplasia of the lymph follicles.

The third case was that of a man aged 33 who complained of "stomach trouble" and mild jaundice. There were numbers of enlarged lymph nodes in both axillas and palpable lymph nodes in the inguinal regions. The spleen was felt 6 cm. below the costal margin on the left side. An abdominal exploration revealed overgrowth of lymph nodes in the retroperitonal region. The nodes were closely packed and varied in size from 1 to 6 cm. Numerous enlarged lymph nodes were observed in the vicinity of the common bile duct; these nodes were thought to have caused jaundice by obstructing the biliary drainage system. A lymph node removed from the abdomen measured 5 by 3 by 1 cm. Histologic examination showed numerical and dimensional hyperplasia of the lymph follicles and moderate streaklike interfollicular fibrosis.

The latter case, presumably the first of its sort to be described, showed preponderant involvement of the abdominal nodes. In later years further evidence has accumulated to show that giant follicular lymphadenopathy is a preponderant or "primary" disease of the deeper lymphoid structures, more especially of the abdominal nodes, and that enlargement of the superficial nodes, when present, is a secondary phenomenon. The massive splenomegaly seen in Becker's case and in one of the cases recorded by Brill, Baehr and Rosenthal serves to support the view that there is probably a primary or a preponderant splenic variety of giant follicular lymphadenopathy.

SYNONYMS

In spite of the fact that giant follicular lymphadenopathy has only recently come to notice, several synonyms have arisen, among them "generalized giant follicular hyperplasia of lymph nodes and spleen," "giant follicular lymphoblastoma" and "giant follicular lymphoma." In addition, an eponymic designation has been introduced—Brill-Symmers disease (Craver, 1934). Since there seems to be no way of including Becker's name and that of Baehr and of Rosenthal without confusing matters still further, it would appear that the eponym is inappropriate and should be abandoned.

INCIDENCE

Giant follicular lymphadenopathy seems to occur almost twice as often in males as in females between the ages of 2 and 80, and most often between the ages of 25 and 40, and apparently prevails with much the same frequency as Hodgkin's disease.

ETIOLOGIC CONSIDERATIONS

The cause of giant follicular lymphadenopathy is unknown. The view that the disease is inflammatory was originally advanced by Brill, Baehr and Rosenthal but has since been modified by Baehr (1932) and by Baehr and Klemperer (1940), who now maintain that it is a form of lymphoblastoma or, as the latter express it, "a benign variety of lymphosarcoma." According to Symmers, giant follicular lymphadenopathy is primarily a toxic or an inflammatory disease which, however, is capable of transforming directly into polymorphous cell follicular sarcoma.

PATHOLOGIC ASPECTS

The little that is known of the pathologic changes characteristic of giant follicular lymphadenopathy is based on the study of lymph nodes excised for biopsy and a few spleens removed at operation and on a total of 5 necropsies.

Lymph Nodes.—In giant follicular lymphadenopathy the nodes vary in size from 1 to 5 cm. or more and are almost always discrete and movable. As a rule, they are rounded or oval. Sometimes individual nodes or small groups of nodes may diminish in size spontaneously or disappear for a while. Occasionally they may break, discharge a thin watery or faintly cloudy fluid and heal slowly. Spontaneous attempts at healing may occur, as shown histologically by patches of granulation tissue, interfollicular fibrosis and sclerotic follicles.

Enlargement of the nodes is due to numerical and dimensional hyperplasia of the lymph follicles. Lymph cords and sinuses are practically always obliterated. Almost every follicle is delimited by a zone of closely set, deeply staining small lymphocytes, laid down in one or more rows which are arranged in orderly sequence and fade gradually into the loosely distributed small lymphocytes of the surrounding parenchyma. The lymph follicles differ in size and shape. Some are massive and others are diminutive; still others are enlarged in varying proportions. They are distributed throughout the substance of the node, differing in this respect from the follicles in physiologic circumstances, in which the distribution is almost exclusively confined to the periphery. For the greater part, the follicles are rounded or oval, but in numerous instances they assume different shapes, of clover leaf, kidney, boat, hook or beak, sometimes with, and at other times without, breaks in the containing wall of small lymphocytes. They may be so closely packed as to occupy almost all of the substance of the node, or they may be set apart at variable distances, the intervening areas consisting of small lymphocytes. Many follicles are indistinguishable from those found in lymph nodes showing the familiar hyperplasia which occurs in association with inflammatory lesions and with both

cancerous and noncancerous neoplasms. At other times in giant follicular lymphadenopathy all the follicles are made up of embryonal cells with large hypochromatic or almost achromatic nuclei and sharply defined, often indented nuclear membranes, the so-called shadow cells, and similar but slightly smaller cells which are somewhat richer in chromatin and the nuclear membranes of which are also indented in such fashion as to give the nuclei curious shapes. The latter cells are believed to be transitional between the large shadow cells and still smaller, richly chromatic cells of the large lymphocyte type, with no detectable limiting membrane and irregular, sometimes angulated nuclei. These several types of cells often lie in a filmlike syncytium and may be present in varying numbers. In certain instances the peripheral zone of small lymphocytes is lacking. In still others the follicles are composed practically exclusively of small lymphocytes. As long as these hyperplastic and variously modified collections of cells remain localized within the lymph follicles, the disease falls under the heading of giant follicular lymphadenopathy, but when the follicles rupture and the cells escape into the surrounding tissues of the lymph node, the disease giant follicular lymphadenopathy transforms directly into polymorphous cell follicular sarcoma.

Terplan (1929) contributed a case of giant follicular lymphadenopathy in which necropsy was done. The cervical nodes were described as about "the size of a bean," as were most of the axillary and supraclavicular nodes, although occasional ones reached the proportions of a "small prune." The superficial and deep inguinal nodes were from "bean to hazelnut size," occasionally "the size of a prune." The retroperitoneal nodes were greatly enlarged, some of them forming clusters the "thickness of one's finger"; others were discrete and ranged in size from that of "a cherry to that of a hazelnut." The spleen was enlarged and measured 20 by 13 by 8 cm. Histologic examination revealed numerous enlarged, pale-staining lymph follicles in all the nodes and in the interstitial tissues of the liver, in the bone marrow and in the spleen. In 2 cases recorded by Symmers the findings at necropsy were almost identical with those described by Terplan except that in 1 case the spleen was not enlarged and in both the bone marrow was intact. In 1 case there was extensive edema of both lower extremities. The abdomen contained 4,000 cc. of chylous fluid. The abdominal aorta, the iliac arteries and the inferior vena cava were embedded in masses of closely packed lymph nodes measuring on an average 3 cm. in their longest diameters. The liver weighed 3,300 Gm. Scattered through it were nodules which varied in diameter from 1 to 10 cm. Approximately four fifths of the liver was replaced in this fashion. The spleen weighed 160 Gm. A third case recorded by Symmers was that of a woman 33 years of age who com-

plained of two symmetrically located "lumps" in the neck, each "about the size of an olive," and of several similar enlargements in the axillas. Nodes were removed Oct. 22, 1936 and again in March 1937. Microscopically, all of them showed numerical and dimensional hyperplasia of the lymph follicles. At necropsy a few enlarged lymph nodes were found in the neck and groins. Several axillary nodes on both sides were enlarged and measured from 2.5 to 5 cm. in their longest diameters, one of them attaining a diameter of 10 cm. The mediastinal lymph nodes were enlarged in moderate numbers. A chain of elongated lymph nodes extended along the line of the external iliac and hypogastric vessels, each node measuring from 3 to 4 cm. in length. The spleen was enlarged and measured 15 by 9 by 3 cm. Microscopic examination of both lymph nodes and spleen showed widespread necrosis of the lymph follicles. In a case of giant follicular lymphadenopathy investigated at necropsy by Cohen and Bergstrom (1946) "all lymph nodes were involved" and the "enlargement was preponderant (or primary) in the mesenteric and retroperitoneal regions."

Spleen.—Splenomegaly has been noted in varying degree in a majority of the cases of giant follicular lymphadenopathy thus far recorded and is due to hyperplasia of lymph follicles. The spleen may vary in size, in some instances approximating the normal and in others being regarded as enormous.

The question whether there is a form of giant follicular lymphadenopathy which arises in the spleen cannot be put at rest until necropsy reveals an enlarged spleen in which the lymph follicles show numerical and dimensional hyperplasia unassociated with extensive enlargement of lymph nodes in other parts of the body due to follicular hyperplasia. A case of possible primary giant follicular lymphadenopathy of the spleen was that of a woman aged 48 who was admitted to Bellevue Hospital Nov. 24, 1937 and again May 3, 1938. On both occasions she complained of tarry stools, which had been present "off and on" for a period of several years, and occasional vomiting of large quantities of bright red blood. The spleen was firm and enlarged, extending about 10 cm. below the costal margin on the left side. There were no signs of enlargement of any of the superficial nodes. Splenectomy was done Jan. 18, 1941. The spleen weighed 800 Gm. and measured 15 by 8 by 5 cm. Scattered through it were large numbers of whitish areas corresponding to hyperplastic lymph follicles.

Decker and Little have published a case in which the spleen weighed 3,500 Gm. and measured 22.5 by 11.3 by 6.5 cm. There was no apparent enlargement of the superficial lymph nodes. On microscopic examination the spleen was found to be riddled by hyperplastic lymph follicles. At the time of operation two enlarged nodes were found in the gastrosplenic omentum, the larger measuring 2 cm. in its longest

diameter. Microscopic examination of this node showed changes which were much the same as those in the spleen. Two years and five months later the patient had no detectable signs of lymph node enlargement in any part of the body.

de Jong has reported 3 cases in which a spleen removed at operation showed enlargement due to hyperplastic lymph follicles. No enlarged lymph nodes were detected in any of these 3 cases.

Appendix.—There is some evidence to show that giant follicular lymphadenopathy may occur as a preponderant or primary lesion of the appendix (Symmers, 1944; Morehead and Woodruff, 1945). In these circumstances the greatly enlarged follicles correspond in practically every particular to those in the lymph nodes of giant follicular lymphadenopathy, including curious configurations, the shape, for instance, of a boat or a kidney or a hook. They may encroach on the lumen and cause almost complete replacement of the mucosa and the muscularis. In 3 cases recorded by Morehead and Woodruff the hyperplastic follicles transformed into polymorphous cell sarcoma.

Cutaneous Changes.—There appears to be a relationship between certain disorders of the skin, especially dermatitis exfoliativa, and lymphadenopathy. At Bellevue Hospital 17 cases of dermatitis exfoliativa were encountered at necropsies. In 4 of these the condition was associated with poisoning by arsphenamine. Among the remaining 13 were 3 cases of Hodgkin's disease, 1 case of tuberculous lymphadenopathy and 2 cases of polymorphous cell follicular sarcoma. Combes and Bluefarb (1941) encountered 15 cutaneous lesions which were associated with giant follicular lymphadenopathy—7 cases of exfoliative dermatitis, 3 of eczema, 4 of discoid and lichenoid dermatitis and 1 case of so-called mycosis fungoides. In 5 of the 15 cases of giant follicular lymphadenopathy, the condition terminated in polymorphous cell sarcoma. Hurwitt, under the heading of dermatopathic lymphadenitis (1942), has reemphasized the occurrence of "widespread skin disease of relatively long duration and generalized superficial lymphadenopathy." The condition observed by him is related to, if not identical with, that described by Symmers, in 1938, in which there is hyperplasia of lymph follicles, with pigment derived from lesions of the skin being deposited in the enlarged lymph nodes. Much the same lymph node changes associated with various diseases of the skin were described by Pautrier and Woringer in 1932 and again in 1937.

PARALLELISMS BETWEEN HODGKIN'S DISEASE AND GIANT FOLLICULAR LYMPHADENOPATHY

There are several parallelisms between giant follicular lymphadenopathy and Hodgkin's disease. Clinically, the two diseases may be easily confused, because in both the first detectable signs of lymph

node enlargement are in the superficial nodes. In both diseases the enlarged superficial nodes may be distributed with almost unlimited diversification—in this respect no 2 cases of Hodgkin's disease or of giant follicular lymphadenopathy ever "look alike." Nevertheless, the clinical resemblance between the two diseases is not to be denied.

For many years the enlarged superficial nodes of Hodgkin's disease were regarded as multiple primary foci. At the present moment the belief is often entertained that the enlarged superficial nodes are outposts stationed at a distance from the main body of enlarged nodes in the deeper parts or from the thymus or the spleen. The opinion seems to be prevalent that the enlarged superficial lymph nodes of giant follicular lymphadenopathy are also multiple primary foci. However, the contrary seems to be true—that giant follicular lymphadenopathy, like Hodgkin's disease, is primarily a disease of the deeper lymph nodes and that the enlarged superficial nodes are outposts, situated at a distance from the main body of enlarged nodes. This conclusion is based on the fact that in giant follicular lymphadenopathy the abdominal lymph nodes, or the abdominal and thoracic nodes combined, are enlarged out of proportion to the superficial nodes, which are comparatively small and few. It has also been shown that there are grounds for the belief that there is a form of primary giant follicular lymphadenopathy of the spleen. Unlike Hodgkin's disease, however, giant follicular lymphadenopathy has not thus far been described as a "primary" disease of the thymus. Although lymph follicles occur in the medulla of the human thymus, they are rare (Wegelin, 1918). Nevertheless it is perhaps not overpresumptuous to predict that giant follicular lymphadenopathy will eventually be described as a "primary" disease of the thymus.

A significant parallelism between Hodgkin's disease and giant follicular lymphadenopathy is that in both diseases the earliest change observed in the node is hyperplasia of the lymph follicles. In Hodgkin's disease the hyperplastic follicles soon disappear and are almost always replaced by lymphoid and other cells of the familiar composite which characterizes this disease; only occasionally is the follicle, or its remnants, retained through the histologic cyclorama. In giant follicular lymphadenopathy, on the other hand, the hyperplastic follicles are usually preserved throughout. Longcope described hyperplastic follicles and follicular remnants in nodes from patients with Hodgkin's disease. To his description may be added the conclusion that the hyperplastic lymph follicle is a prerequisite for the development of Hodgkin's disease. If this is true, it establishes not only another important resemblance between Hodgkin's disease and giant follicular lymphadenopathy but a fundamental relationship between them and between all those diseases which are conceived in hyperplasia of lymph follicles. This

conclusion is supported by the fact that signs of giant follicular lymphadenopathy, polymorphous cell follicular sarcoma and Hodgkin's disease sometimes exist side by side in the same lymph node and by the fact that lymphosarcoma, lymphoid leukemia and pseudoleukemia are also initiated by hyperplasia of lymph follicles. This is not meant to imply that there is a fundamental relationship between all diseases in which hyperplasia of lymph follicles occurs, but between all lymphoid diseases and not between all diseases affecting the lymphoid system. It does not apply, for example, to tuberculous lymphadenopathy with secondary hyperplasia of lymph follicles; or to syphilis of the lymph nodes; or to Gaucher's disease of the spleen, lymph nodes, liver and bone marrow; or to that stage of infectious mononucleosis in which lymph follicles multiply and enlarge, and so on. These are diseases that affect the lymphoid system but are not lymphoid diseases.

Another parallelism between Hodgkin's disease and giant follicular lymphadenopathy is that spontaneous diminution or even disappearance of the enlarged lymph nodes may occur in both and that in both the enlargement is almost certain to recur sooner or later.

In contrast to the parallelisms mentioned, giant follicular lymphadenopathy and Hodgkin's disease display certain antipodal peculiarities which are of some importance in the interpretation of the nature of the two diseases. For example, in giant follicular lymphadenopathy eosinophils are seldom present in the peripheral blood either in high normal or in abnormal numbers. This would seem to indicate no noteworthy increase in the activity of the bone marrow. In Hodgkin's disease eosinophils are frequently present in the peripheral circulation in high normal numbers and sometimes in high abnormal numbers. They have been recorded as constituting as much as 60 per cent of the total number of leukocytes of the peripheral blood. They are also detectable in a large percentage of all microscopic preparations of lymph nodes and may be found in association with eosinophilic myelocytes. These findings and the increased numbers of polymorphonuclear neutrophils and platelets of the peripheral circulation are indicative of a degree of activity noticeably transcending that of the normal in the bone marrow.

TRANSFORMATIONS OF GIANT FOLLICULAR LYMPHADENOPATHY

The direct transformation of the relatively benign disease giant follicular lymphadenopathy into a cancer capable of widespread destruction of tissues, on the one hand, and into Hodgkin's disease, on the other, are developments that have been described only within recent years. Clinically, the transformations are insidious and present at the outset no signs by which they may be detected or even suspected. If under radiation therapy the lymph node enlargements in giant follicular

lymphadenopathy do not regress quickly, one should suspect that the condition is undergoing some form of mutation, more especially that leading to polymorphous cell sarcoma or to Hodgkin's disease. It has also been shown in recent years that giant follicular lymphadenopathy may transform directly into a rapidly fatal disease of lymph nodes and spleen, attended by acute necrotic folliculitis, and into lymphoid leukemia (Symmers, 1938). All of these transformations emphasize the necessity for early diagnosis of giant follicular lymphadenopathy and immediate resort to appropriate methods of therapy.

Giant Follicular Lymphadenopathy Transformed into Polymorphous Cell Sarcoma.—Polymorphous cell sarcoma is derived directly from the hyperplastic lymph follicles of giant follicular lymphadenopathy. Histologically, the growth is characterized by the presence of ruptured follicles and cellular infiltration of the parenchyma of the node. The infiltrating cells are of three types: one with a large hypochromatic indented nucleus, the so-called shadow cell; one with a slightly smaller and more richly chromatic, similarly indented nucleus that is transitional between the large hypochromatic or shadow cell and the hyperchromatic type of the large lymphocytes. All the three types of cells lie in masses of homogeneous, structureless syncytium. Anatomically, cases of polymorphous cell sarcoma are divisible into two groups—one group in which the sarcomatous changes are confined to the lymphoid tissues, preponderantly the lymph nodes, while the spleen may or may not be involved, and a second group in which the changes seen in the lymph nodes and the spleen are accompanied by similar alterations in organs not customarily included in the lymphoid system, among them the lungs, the pleura, the kidneys and the adrenal glands, and by destructive lesions of bone, which give rise to spontaneous fractures (Symmers, 1942; Kenney, 1945).

A case of the latter description was that of a man aged 48 who complained of weakness and pains in the legs of eight months' duration and of inability to walk. Physical examination revealed atrophy of the muscles of the lower extremities. A neurologist commented that the "evidence indicates involvement of the cord and peripheral nerves." At necropsy there was marked axillary and inguinal adenopathy. Enlarged lymph nodes were found on the upper surface of the diaphragm, in the anterior and superior mediastinum, in the tissue surrounding the great vessels of the neck and in the axillary regions. The pleura of both sides was irregularly thickened owing to the numerous nodules present in the parietal layer. It was estimated that these nodules covered about 30 per cent of the pleural surface. Many of the pleural nodules replaced the intercostal muscles and infiltrated the adjacent ribs. The aorta and the inferior vena cava lay in a bed of enlarged lymph nodes, which were adherent to one another in the region of the lower lumbar vertebrae, where the individual nodes measured up to about 5 cm. in diameter. The external iliac and femoral arteries were similarly surrounded, and the psoas major muscles were infiltrated by tumor tissue. The lower lumbar vertebrae were largely replaced by tumor infiltrate, as were the ilia, the lateral portions of both clavicles and a trochanter of the right femur. The spleen weighed 195 Gm. At

the upper pole was a tumor nodule which projected above the surface to the extent of 1.5 cm. The cortex of the left adrenal gland showed a nodule, which measured 1.5 cm. in width and 6 mm. in thickness. A nodule in the left kidney measured 1.5 cm. in width and the upper portion of the pelvis was almost completely replaced by a tumor which projected into the medulla for a distance of 1 cm. and invaded the peripelvic fat.

Giant Follicular Lymphadenopathy Transformed into Hodgkin's Disease.—Since it is known that Hodgkin's disease is initiated by hyperplasia of lymph follicles, it follows that giant follicular lymphadenopathy, which is similarly initiated, should, as it were, offer prepared ground for the development of Hodgkin's disease. This transformation of the disease occurs and is believed to be brought about by the same process by which lymph nodes are transformed into Hodgkin's disease without the intervention of the disease giant follicular lymphadenopathy; that is to say, by a process of embolism of megakaryocytes and other cells derived from the bone marrow, which are deposited in the modified nodes.

Giant Follicular Lymphadenopathy Transformed into Lymphoid Leukemia.—In addition to other peculiarities of behavior, giant follicular lymphadenopathy shows a propensity for ending life by the process of being transformed into lymphoid leukemia. Four cases of this sort have been described by Symmers.

In one case a man aged 38 complained of progressive weakness of nine months' duration. There were 30 or more enlarged lymph nodes in the neck, some of which measured 2 cm. in their longest diameters. Similarly enlarged lymph nodes were found in the axillas, in the groins and along the course of the saphenous vein on each side. The spleen was enlarged, reaching almost to the level of the left ilium, whence it could be traced upward and inward to within 3 or 4 cm. of the median line. Microscopic examination of excised lymph nodes showed them almost completely replaced by hyperplastic follicles. At the outset of the disease numerous blood counts showed progressive secondary anemia. Several months later it was found that the white cells numbered 23,300, of which 92 per cent were lymphocytes.

SYMPTOMS AND SIGNS

Giant follicular lymphadenopathy or its associated disease, polymorphous cell follicular sarcoma, is attended by relatively few symptoms and signs. Symptoms are rare. Signs may be obvious in the form of discrete enlargement of superficial lymph nodes or enlargement of the spleen or both. In the later stages signs referable to interference with the venous return may be shown by serous effusions or edema of the extremities. Blood changes are limited, as a rule, to leukopenia without noteworthy alterations of the differential count of the white cells. Peripheral eosinophilia is rare. Thus far no significant or constant disturbances of temperature have been recorded, although a Negro patient, a boy 12 years of age, presented a febrile temperature curve

noticeably like that of the Murchison type of remittent fever. Enlargement of the superficial lymph nodes in company with various chronic disorders of the skin, especially dermatitis exfoliativa, should arouse suspicion of giant follicular lymphadenopathy or polymorphous cell sarcoma, although similar changes may occur in the skin in Hodgkin's disease.

DIAGNOSIS

There is but one method of arriving at a correct diagnosis of giant follicular lymphadenopathy or polymorhous cell follicular sarcoma of lymph nodes and that is by the process of biopsy. If practicable, more than one lymph node should be removed, because one node may show, on histologic examination, the changes of giant follicular lymphadenopathy while its nearest neighbor may be the seat of a polymorphous cell follicular sarcoma. Moreover, the combined changes of giant follicular lymphadenopathy and polymorphous cell sarcoma may sometimes occur in one and the same lymph node together with the histologic signs of Hodgkin's disease.

TREATMENT

At Bellevue Hospital radiation is used in the treatment of giant follicular lymphadenopathy as a routine. The rays employed are generated at 200 kilovolts and filtered through 0.5 mm. copper plus 1 mm. aluminum or through a Thoraeus filter at a distance of 50 cm. The size of the portal is adapted to that of the area of involvement and varies from 50 to 400 sq. cm. Unit doses of from 150 to 200 roentgens (in air) are administered daily or on alternate days. A total dose of 800 to 1,000 r is usually adequate to cause recession of the enlargement of nodes or of spleen. Lymph nodes which have been transformed into polymorphous cell sarcoma require higher doses, and the same factors are employed, continuing up to 2,000 to 3,000 r. An alternate technic permits the unit dose to be increased up to 300 r to shorten the treatment cycle while delivering the prescribed total dose (Rubenfeld, 1947). In the comparatively short interval of twenty-one years during which radiation has been employed against giant follicular lymphadenopathy, the efficacy of this form of therapy, even in the absence of a control series of untreated patients, is indicated by the fact that 10 patients are apparently well after three, four, four and one-half, five, five, seven, nine and one-half, ten, twelve and fourteen years. Five patients with polymorphous cell sarcoma are apparently well after four, seven, eight, eight and twelve years.

LYMPHOID LEUKEMIA

In October 1845 Hughes Bennett described a chronic disease characterized by "suppuration of the blood, with enlargement of the spleen and liver." A month later Virchow recorded a disease, also chronic,

in which he noted that excessive numbers of blood leukocytes were attended by splenomegaly. Ehrlich named the disease lymphoid leukemia.

INCIDENCE

Chronic lymphoid leukemia is relatively rare before the age of 25 and is commoner in males in the proportion of about 5 to 1. The acute variety is commonest in the early years of life. In rare instances, chronic lymphoid leukemia has been described as occurring in persons over 70 years of age. The disease is of wide geographic distribution, and no race is exempt.

ETIOLOGIC CONSIDERATIONS

Familial and hereditary factors, trauma, infections (including tuberculosis), animal parasites, drugs, radioactive substances and other agents have been invoked as contributory causes of lymphoid leukemia, but the exciting cause is unknown. There are two theories concerning the nature of leukemia. One holds that the disease is a primary malignant neoplasm of the lymphoid system and that the immature lymphocytes seen in the blood stream are circulating metastases. This point of view, if accepted, still leaves the cause of leukemia in doubt. The second theory holds that leukemia is an infective process. The rapidity with which acute leukemia terminates life suggests the validity of this view, but chronic leukemia seems not to permit the same interpretation.

PATHOLOGIC ASPECTS

It is accepted that the lymphocytes originate in the germinal centers of the lymph follicles, that lymph follicles exist in greatest numbers in the lymph nodes and in second greatest numbers in the spleen, the auxiliary lymphoid system participating in greater or less degree. Histologically, chronic lymphoid leukemia consists of hyperplasia of lymphoid cells, which extend outward from the edges of the enlarged and numerically increased follicles, completely replacing the normal structure of the nodes. The majority of the cells are small lymphocytes. As the process advances, the follicles tend to disappear, but even in circumstances of extreme hyperplasia of small lymphocytes an occasional intact follicle or follicular remnants may persist. In acute lymphoid leukemia the lymph follicles disappear early and follicular remnants almost never remain.

Lymph Nodes.—The lymph nodes in both acute and chronic lymphoid leukemia are practically always enlarged in groups or chains. The nodes are discrete although closely packed, separate enlargements occurring comparatively rarely. They vary in size from a few millimeters to 8 or 10 cm. or even more. Their shape depends on their

proximity, one to another. When closely packed they assume such shapes as are determined by the effects of reciprocal pressure, seldom by the pressure that they themselves exert against neighboring solid or resisting tubular structures. Each node is invested by a thin connective tissue capsule. The substance is soft or of slightly increased consistency, depending on the amount of connective tissue present, which is almost never excessive. As a rule, the substance of the node bulges slightly beyond the cut edge of the capsule, especially in acute lymphoid leukemia, and is whitish or cream colored, often speckled by reddish dots or streaks corresponding to the distribution of red blood cells lying in capillary vessels or to hemorrhages. Sometimes fusion of nodes occurs.

In the presence of chronic lymphoid leukemia it is possible to arrive at a reasonably safe conclusion concerning the age of the aggregate of enlarged lymph nodes as compared with the age of the estimated sum total of hyperplastic lymph follicles of the spleen by guesswork based on relative sizes, and in this way to speculate on antecedence of origin. If the spleen is greatly enlarged and the aggregate of enlarged lymph nodes is correspondingly small, it is justifiable to assume that the changes in the spleen preceded those in the lymph nodes. If the aggregate of enlarged lymph nodes appears to be greatly in excess of the estimated sum total of the hyperplastic lymph follicles of the spleen, it is equally justifiable to assume that the hyperplastic changes in the lymph nodes preceded those in the spleen. If the aggregate of enlarged lymph nodes appears to be much the same as the sum total of the hyperplastic lymph follicles of the spleen, it may be assumed with like propriety that the lymphoid hyperplasias of the two localities commenced at the same or approximately the same time.

In the laboratories of pathology of Bellevue Hospital 36 cases of chronic lymphoid leukemia were encountered among 22,537 necropsies (Symmers, 1944). Studies based on these cases confirm with monotonous regularity the descriptions of the anatomic changes of the disease as portrayed in current texts. In addition, certain features were brought out which no doubt have been mentioned before as individual examples but appear not to have been emphasized as a whole. Reference is made to the comparisons of the aggregate of lymph node enlargements and the size of the spleen as indicating in given cases whether the disease arose or attained preponderance in the lymph nodes or in the spleen.

Current texts on medicine and pathology are apt to lead one to believe that enlargement of the superficial lymph nodes is a frequent, if not a constant, and the preponderant, anatomic feature of chronic lymphoid leukemia. According to the records of the necropsies performed at Bellevue Hospital, this seems not to be true. Of 36 cases, the superficial nodes were not enlarged in 4 (11 per cent) and were

enlarged only slightly in 9 (25 per cent), moderately in 18 (50 per cent) and massively in 5 (14 per cent). The thoracic nodes were not enlarged at all in 18 cases (50 per cent) and were slightly enlarged in 3 (8.3 per cent) and massively enlarged in 15 (41.7 per cent). The retroperitoneal nodes alone were involved in 12 cases (33 per cent), eight times massively (22 per cent) and four times moderately (11 per cent). The retroperitoneal and mesenteric nodes together were massively enlarged in 13 cases (36 per cent). The mesenteric nodes alone were involved in 5 cases, three times massively and twice moderately. The abdominal and thoracic nodes together were enlarged in 17 of 36 cases (47 per cent), massively in 16 (44 per cent). In 6 cases (16 per cent) the abdominal nodes were not enlarged at all.

The weight of the spleen was recorded in 32 of the 36 cases. The smallest spleen weighed 250 Gm. It was found in a 65 year old woman with preponderant enlargement of the thoracic and abdominal nodes and innumerable focal lymphomas in a liver weighing 1,880 Gm., together with generalized superficial lymphadenopathy. The largest spleen weighed 2,500 Gm. and extended downward to the brim of the pelvis and inward to the midline. It was found in a white man aged 32 and was accompanied by "about 100" retroperitoneal lymph nodes measuring from 0.5 to 2.5 cm. in their longest diameters. There were no enlarged superficial or thoracic nodes.

The average weight of the spleen in 32 cases was 887.96 Gm. In one of the 4 remaining cases the spleen was described as "slightly enlarged." In the other 3 it measured 18, 21 and 22 cm. in length. The spleen was preponderantly or "primarily" enlarged in 10 cases. In 3 of these cases the superficial lymph nodes were not enlarged. In the 10 cases, with the three exceptions noted, there were various combinations of enlarged superficial, thoracic and abdominal nodes. However, the aggregate of these did not approach the estimated sum total of the hyperplastic lymph follicles of the spleen. From this it seems that in one group of cases lymphoid leukemia shows itself in the form of preponderant or "primary" enlargement of the abdominal lymph nodes, followed by enlargement of the spleen, and that in a second group it produces preponderant or "primary" enlargement of the spleen, followed by enlargement of the lymph nodes of the abdomen alone or of those of the abdomen and those of the chest together. In other words, in the Bellevue Hospital necropsy experience lymphoid leukemia is preponderantly or "primarily" a disease of the abdominal lymphoid organs. According to the same experience, lymphoid leukemia does not produce preponderant changes in the lymph nodes of the thorax or in the superficial nodes. When these two groups of lymph nodes are enlarged at all, it is apparently a late sign of preponderant involvement of the abdominal nodes alone, or of the abdominal and thoracic

nodes combined, or of the spleen alone or combined with the abdominal or the thoracic nodes, or with both groups of nodes. Preponderant enlargement of the thoracic nodes alone does not occur, according to necropsy experience at Bellevue Hospital.

Gastrointestinal Tract.—In 14 cases of the Bellevue Hospital series the solitary and agminated follicles of the intestinal tract were hyperplastic alone or in combination with one another. In the majority of instances these involvements were almost negligible anatomically, and consisted of slight or moderate hyperplasia of the lymphoid follicles, most marked in the ileum but not confined to that region. In some of the cases Peyer's patches were hyperplastic, occasionally attaining a length of 5 cm. In a few instances they were superficially ulcerated. In 2 cases the intestine was affected to an extraordinary extent and, indeed, the changes appeared to be unique as far as true lymphoid leukemia is concerned, but were replicas in miniature of those that occur in the gastrointestinal variety of so-called pseudoleukemia.

One of these cases was that of a Negro, a man aged 31. The cervical, axillary and inguinal nodes were slightly enlarged. There were "one or two enlarged peribronchial nodes"; otherwise the thorax was free from lymph node enlargements. The mesenteric and retroperitoneal nodes were numerous and discrete, and varied in diameter from 0.5 to 2.5 cm. The spleen was enlarged, measuring 21 by 7 by 6 cm. Its weight was not recorded. From the beginning of the duodenum to the anus the mucous membrane of the intestine was elevated by countless numbers of hyperplastic follicles. They were most numerous in the ileum, especially in its lower two thirds. All of Peyer's patches were hyperplastic.

In a second case, that of a boy 13 years of age, dead of acute lymphoid leukemia, the ileum showed numerous transverse ulcers varying from 1 to 2 cm. in length. The edges were elevated to the extent of about 2 mm. The craters were grayish, in places necrotic, in other places freshly hemorrhagic. Some of the ulcers in the upper part of the ileum were superficial. Most of those in the lower one third of the ileum were deep and extended through the musculature to the serosa, which was edematous, injected and covered by fibrinous exudate. There were no perforations. Microscopically, the ulcers were rimmed by closely packed lymphocytes, sometimes mixed with red cells or with small deposits of fibrinoid material. Peyer's patches were unaffected except for a mild degree of hyperplasia and an occasional area of superficial ulceration.

In only a few of the 40 necropsies performed at Bellevue Hospital in cases of lymphoid leukemia was it permitted to remove the structures of the mouth and throat. However, it was noted in 2 cases that the lingual tonsils were markedly hypertrophied and that the faucial tonsils were hypertrophied in a single case. In only 1 of the 40 cases was lymphoid hyperplasia of the stomach encountered. In that case the lymph follicles of the pyloric end were hyperplastic. In still another case the lymph follicles of the esophagus projected beneath the mucosa in considerable numbers.

Thymus.—For a good many years opinion was divided as to whether the small cells of the thymus are lymphocytic or epithelial. The consensus now is that the thymus is a lymphoid organ and that only the large reticulum cells which are distributed through the parenchyma, and which enter into the formation of Hassall's corpuscles, are epithelial structures. It remains to trace the relationship, if any, of the thymic lymphocytes and lymphoid leukemia. Whether in these circumstances the enlarged thymus is a lymphocytogenic organ that contributes to the leukemic process, or whether in lymphoid leukemia the thymus enlarges because it is infiltrated by lymphocytes from the blood stream, seems open for discussion. One of the cases in the Bellevue Hospital series tends to throw some light on this phase of the subject:

The case was that of a Negro, a man 35 years of age. The superior mediastinum was occupied by the thymus gland, which lay in the midline. The gland measured 8 cm. in length and weighed 48 Gm. The organ was pink, and the notched apex pointed downward. On microscopic examination the normal markings of the thymus were submerged by infiltrating lymphocytes, among which were the remains of a few Hassall's corpuscles. In the immediate vicinity of the thymus were dozens of discrete lymph nodes measuring 0.5 to 3 cm. in their longest diameters. The spleen weighed 640 Gm. and was rich in lymphoid cells. The retroperitoneal nodes were enlarged, forming masses in which the individual nodes measured from 0.5 to 5 cm. in diameter. The pancreas was almost obliterated, partly by pressure of neighboring lymph nodes and partly by interstitial lymphocytic infiltration. Thus it appears that in the thymus gland the changes were moderate as compared with those in the lymph nodes and the spleen, and that the thymus was a participant in, rather than a source of, the leukemic process.

Liver.—In 21 of the 36 cases of chronic lymphoid leukemia comprising the Bellevue Hospital series the liver was weighed. In another 3 cases the liver was described as "normal in size," "enlarged" and "markedly enlarged." The smallest of the 21 livers weighed 1,230 Gm., the largest, 3,900. The average weight was 2,389.52 Gm. or about 800 Gm. above the average weight for adult males, which is usually placed at 1,500 Gm., or a few grams above the average for adult females. In only one of the 4 cases of acute lymphoid leukemia was the weight of the liver recorded. It was described as large, weighing 750 Gm. The patient was a 3½ year old child.

In chronic lymphoid leukemia the liver shows whitish areas corresponding to lymphoid deposits. They occur with greatest frequency in the perilobular connective tissue and vary in size from minute foci to nodules which project above the surface and expand to produce pressure atrophy of neighboring lobules. In the perilobular tissues the lymphoid deposits are practically never attended by the formation of follicles. They seem to represent a combination of cells produced by hyperplasia of normally resident lymphoid collections and lymphocytes derived from the blood stream.

Kidneys.—Of the 40 cases of lymphoid leukemia investigated by necropsy at Bellevue Hospital, the kidneys were involved in 10 (25 per cent). In 7 cases the organs were not enlarged, although all were diffusely infiltrated by lymphocytes. In one of the 3 remaining cases each kidney was enlarged and measured 14 by 7.5 by 4 cm., and both organs were richly infiltrated by lymphocytes. In a second case the kidneys together weighed 450 Gm., and in a third case, 900 Gm. In both cases the kidneys were extensively infiltrated. In all of these cases the lymphocytes lay in the connective tissues. In some instances they were more or less loosely sprinkled. In other cases the structures of the kidney from capsule to pelvis were buried in densely packed lymphocytic collections. In not a single instance were functional disturbances recorded which were referable to the changes described, with the exception of 2 cases in which the urine showed an excess of albumin.

Pleurae, Bronchi and Lungs.—In lymphoid leukemia the pleura, the bronchi and the lungs, like all other vascularized structures, are necessarily involved, at least to some degree, by lymphocytic infiltration. That these structures are sometimes extensively concerned, even to the point at which their condition participates in the cause of death, was exemplified by 5, or 12.5 per cent, of the Bellevue Hospital cases.

One case was that of a man aged 27. His body presented a retrosternal mass of enlarged lymph nodes attended on the left by a pleura thickened to the extent of about 2.5 cm The right pleura was thickened to a lesser degree, and the pericardium was similarly involved. On the left side, thickening of the pleura was further apparent as coarse bands following the interlobar septums of the lung.

A second case was that of a boy aged 16 whose body showed at necropsy enlargement of all the superficial lymph nodes and slight enlargement of many paravertebral and mesenteric nodes. The spleen was enlarged, measuring 18 by 10 by 6 cm., and contained numerous but indistinct collections of lymphoid cells. In the superior mediastinum was a solid mass which measured 9 cm. in length and 5 cm. at its points of greatest breadth. Although it occupied the position and resembled the shape of the thymus, it could not be identified as such on microscopic examination. At the bases of both lungs the smaller bronchi were surrounded by grayish tumor-like tissue. Microscopic examination showed, in addition to peribronchial lymphocytic infiltration, patches of lymphocytes scattered through the interstitial tissues and areas of lobular consolidation due to lymphocytic collections in the alveoli and bronchioles.

A third case was that of a Negro, a man 30 years of age. At necropsy a large, ill defined grayish patch was found in the upper lobe of the left lung. A similar patch was present in the upper lobe of the right lung. On microscopic examination both were found to consist of lymphoid cells.

In another man, who was 36 years of age, the upper lobe of the right lung showed an even larger area of consolidation which was likewise due to deposits of lymphocytes.

A fifth case was that of a man 68 years of age in whom at necropsy the anterior mediastinum was almost completely filled by enlarged lymph nodes. Immediately under the thickened and infiltrated pleura covering the lower lobe of the right lung

the walls of the smaller bronchi and the adjacent parenchyma were occupied by whitish tumor-like tissue which on microscopic examination was found to be composed of infiltrated lymphocytes.

Bones.—Infiltration of the periosteum may take place in such manner as to cause elevation of the membrane and erosion of the cortex of the bone. In one of the cases at Goldwater Memorial Hospital there was extensive periosteal and perichondrial infiltration at the junction of the manubrium and the body of the sternum and at several sternocostal articulations. Infiltration of the medullas of bones may produce so-called lymphoid thromboses, resulting in disintegration of the cancellous bone and sometimes in spontaneous fractures. The bones most frequently involved are the femur, the humerus and the vertebra.

SYMPTOMS AND SIGNS

As a rule, the onset of leukemia is insidious, although instances are known in which the disease commenced suddenly with epistaxis or other signs of hemorrhage, especially bleeding of the gums or the stomach. This is oftenest true of the acute leukemias. Bloody diarrhea should arouse suspicion of leukemic ulceration of the intestinal tract. In many instances the patient's attention is first focused on enlargement of the abdomen. This is due either to involvement of the regional lymph nodes, with or without ascites, or of the spleen or of both. In some cases stitchlike pains occur in the left upper quadrant and are due to peripheral lymphoid thromboses occurring in the spleen, followed by localized inflammatory changes in the capsule and irritation of the adjacent peritoneum. In other instances the patients seek advice because of enlargement of the cervical or other superficial lymph nodes. As the disease progresses secondary anemia supervenes. Defective vision may occur because of hemorrhagic extravasations or leukemic infiltrations occurring in the retina. Deafness is a frequent feature. Symptoms of Ménière's disease may be associated with hemorrhagic or infiltrative changes in the semicircular canal. Priapism due to stasis of blood in or lymphoid thrombosis of the corpora cavernosa is a fairly common occurrence and may persist for days or even weeks. Persistent generalized pruritus may precede the appearance of detectable enlargement of the lymph nodes or the spleen for weeks or months. This is especially true of chronic lymphoid leukemia. Fever is commonly present, the temperature ranging from 102 to 103 F. Periods of pyrexia may alternate with intervals of apyrexia.

DIAGNOSIS

The diagnosis of leukemia is determined practically exclusively by the results of the blood examination. The total leukocyte count may vary from 12,000 or 15,000 to several hundred thousand cells per cubic millimeter. The preponderating cell is the immature lymphocyte. An

important point, sometimes overlooked in the diagnosis of leukemia, is that the total leukocyte count may be within or below the normal range, while the percentage of immature leukocytes remains persistently high —that leukocytosis is not necessary for suspecting the existence of leukemia.

TREATMENT

While almost every conceivable therapeutic measure has been used in combating leukemia, none is of much avail; however, the value of radioactive substances remains to be determined. Thus far it appears that no patient with leukemia has been known to recover, either spontaneously or under treatment. The acute disease is almost always fatal within six weeks to three months. The chronic form lasts on an average of about three years. Cases of chronic lymphoid leukemia have been reported with a survival period of twenty-two years (Minot and Isaacs). The patient of Richards and Moench (1942) was alive at the end of sixteen years, during which time he received no special treatment and was in relatively good health.

LYMPHOSARCOMA

Kundrat, who first described lymphosarcoma, defined it as a malignant tumor of lymph nodes or of other lymphoid structures in which lymphocytes proliferate diffusely in an inconspicuous stroma of connective tissue. He noted the tendency of the growth to confine itself within more or less well defined limits. Of 17 cases of lymphosarcoma encountered among 11,925 necropsies at Bellevue Hospital, 9 illustrated Kundrat's maxim of local growth; the remaining 8 displayed no inclination to spare regional or other tissues.

Both from the clinical and from the anatomic standpoint, cases of lymphosarcoma seem to be best presented in five groups: one, cases characterized by involvement of paired organs, among these the breasts, the ovaries, the testicles, the adrenal glands and the kidneys; a second, cases in which regional collections of superficial lymph nodes are involved, notably the cervical nodes, less often the inguinal and axillary nodes; a third, cases in which the lymphoid structures of the thorax, especially the thymus or its remains, and the lymph nodes in the superior mediastinum and at the root of the lung are implicated; a fourth, cases of Sternberg's leukosarcoma, which is manifested as lymphoid tumors of the thymus, the breast, the stomach, the intestines and other tissues, the growths eventually pouring lymphocytes into the blood to terminate life by acute leukemia, and a fifth, the most frequent of all cases, in which the lymphoid tissues of the abdomen, including the stomach, the intestines and the retroperitoneal and mesenteric lymph nodes, are involved.

INCIDENCE

In a series of 100 cases recorded by Kundrat, Ghon and Roman, MacCallum and Symmers, lymphosarcoma occurred predominantly in the following situations: gastrointestinal tract (36 cases), thymic remains (21), cervical nodes (14), abdominal nodes (11), pharynx (7), tonsil (3), mouth (2), inguinal nodes (2), spleen (1), axillary nodes (1), thoracic nodes (1) and prostate (1). In other words, the tissues of the deeper lymphoid structures were preponderantly or "primarily" concerned in 70 cases, including, in the order of their frequency, the gastrointestinal tract, the thymus, the abdominal lymph nodes, the spleen and the thoracic nodes.

In the Bellevue Hospital series there were 14 males and 3 females; the youngest patient was a boy aged 16 and the oldest a man of 63. The disease was encountered oftenest in patients between 30 and 50 years.

ETIOLOGIC CONSIDERATIONS

The exciting cause of lymphosarcoma is unknown. The nature of the disease is debatable. That its clinical behavior is that of a malignant tumor is not to be denied in view of the fact that it may expand mechanically and cause local destruction of tissues. It apparently lacks, however, the ability to metastasize. On the other hand, it seems that the growths in lymphosarcomatosis have multiple foci of origin and arise in previously existing lymphoid depots, the initial changes consisting in hyperplasia of lymph follicles.

Almost every hyperplastic disease of lymphoid tissues, including lymphosarcoma, has been ascribed to the activity of the tubercle bacillus. Ewing, on page 421 of the fourth edition of his book, "Neoplastic Diseases," defines lymphosarcoma as a "true malignant neoplasm." On page 430 of the same edition he states that "tuberculosis occupies a prominent position as an excitant of lymphosarcoma." The view that an infective agent may be an excitant of a cancerous growth is not in accord with the more or less universal belief that such tumors are not infective diseases. However, there seems to be no reason why tuberculosis and lymphosarcoma should not occur together without invoking the relation of cause and effect. That tuberculosis probably has no part in the production of lymphosarcoma is indicated by the fact that in 17 cases investigated by necropsy at Bellevue Hospital the association was not noted in a single instance.

The Contagious Lymphosarcoma of Dogs.—According to DeMonbreun and Goodpasture, "transmissible lymphosarcoma of dogs is generally considered to be a highly contagious venereal disease, world-wide in its distribution." Transmission is by coitus. In a review of 585 tumors of dogs, Auler and Wernicke encountered the disease

eight times. The primary growth is located either on the glans penis or in the vaginal wall. In the female the primary lesion usually forms a pedunculated mass several centimeters in diameter, which often projects from the vagina. In the male the affected glans is enlarged, is usually eroded and tends to bleed easily. Metastatic nodules may develop in the subcutaneous tissues of the groin, in the retroperitoneal lymph nodes and in the liver and the spleen. Spontaneous recovery of dogs bearing naturally acquired tumors occurs rarely, if at all.

The transmissibility of the disease was first demonstrated by Novinsky, who removed a tumor from the vagina of a bitch and succeeded in inoculating the disease in the subcutaneous tissues of 3 puppies. Wehr also succeeded in transferring the disease and observed that many of the transmitted tumors disappeared spontaneously. Smith and Washbourn inoculated 13 dogs by subcutaneous transplantation. The transplanted tumors reached their maximum sizes about three months after inoculation, at which time they measured from 3.8 to 7.5 cm. in diameter. In several instances complete regression of the transplanted tumors occurred soon after their maximum growth was attained. Spontaneous regression of growths which are acquired by natural means does not seem to occur.

De Monbreun and Goodpasture hold that contagious lymphosarcoma of dogs is a "true neoplasm." To make a polemic of this point would immediately involve the disputants in the inevitably futile discussion as to just what a "true neoplasm" is. However, it is difficult to classify a growth which is transmissible by natural physical contact and does not undergo subsequent spontaneous regression and may even "metastasize" but which when transmitted by artificial means does undergo subsequent spontaneous regression and shows no tendency to "metastasize." It does not correspond in its clinical behavior to that form of new growth which is ordinarily regarded as a "true neoplasm." Some other explanation must be sought, and it would seem defensible to assume that the disease belongs among the infections—that, possibly, it is a virus disease. If the assumption that the transmissible lymphosarcoma of dogs is an infective process is allowed, it might be granted with equal justice that lymphosarcoma in man is likewise infective—that, possibly, it is a virus disease. Although no one has thus far been able to demonstrate that lymphosarcoma is transmissible from man to man or that the human variety can be reproduced in lower animals, this does not argue that it is not transmissible or that it is not infective. It is hazardous to compare a disease which occurs naturally in man with an apparently related disease which occurs naturally in dogs and is not transmissible to man but is transmissible among dogs by direct contact. It nevertheless seems reasonable to consider the possibility that the easily transmissible lymphosarcoma of dogs is an infection of exalted

virulence, and that lymphosarcoma of man is likewise transmissible to one of the same species but that its degree of infectivity is low and its method of transmission well concealed.

PATHOLOGIC ASPECTS

Lymph Nodes.—In lymphosarcoma the lymph nodes present much the same naked eye appearances as in Hodgkin's disease. The individual nodes vary in size from a few millimeters to many centimeters and may be arranged in groups or chains. The nodes are usually closely packed, and their shapes may be altered by pressure, reciprocal or otherwise. When dissected they are found to be discrete, and the more easily accessible nodes are apt to give this impression when palpated through the overlying structures. Their consistency varies and is determined by the amount of connective tissue in them. As a rule, they are relatively soft, because the stroma is seldom abundant. Each is surrounded by a thin capsule, and filmlike sheets of connective tissue insinuate themselves between the nodes. The substance of the node bulges somewhat beyond the cut edge of the capsule. The substance varies in color from dead white or grayish white to a faint brownish sheen but may present a pinkish hue if the delicate connective tissue supporting stroma is well supplied with capillary blood vessels. On microscopic examination the lymph nodes show overgrowth of lymphocytes lying in the connective tissue reticulum. The normal structure of the nodes is obliterated. The capsule is often infiltrated by the same sort of lymphocytes which prevail in the parenchyma, and even the internodal connective tissues may be invaded.

In those comparatively rare cases of lymphosarcoma in which the lymph follicles are not completely obliterated, the lymphocytes which lie in immediate proximity to the germinal centers are slightly larger than the familiar small lymphocytes, and their nuclei are finely stippled. In one group of cases this type of lymphocyte retains its morphologic character throughout and infiltrates the substance and the capsule of the node to form the so-called large cell lymphosarcoma. In a second group of cases the prevailing lymphocyte is noticeably smaller and its nucleus is densely chromatic and almost completely fills the body of the cell. This is the type of cell which proliferates to form the so-called small cell lymphosarcoma. A third type of "lymphosarcoma" has been described under the title of "reticulum cell lymphosarcoma." It is supposed to arise from reticulum cells in the germinal centers of the lymph follicles as well as from those in the parenchyma of the node, but in view of the fact that the relationship of the reticulum cell and the lymphocyte, if any, seems not to be known, it would appear advisable to designate the tumor in question a "reticulum cell sarcoma" of lymph nodes.

Spleen.—In 7 of the 17 cases of lymphosarcoma in the Bellevue Hospital series (41 per cent) the spleen was enlarged. The average weight was 459 Gm. or 259 Gm. in excess of the high normal weight of the spleen of the adult. In 4 cases (23 per cent) the enlargement was due to chronic passive congestion dependent on defective heart action or on local obstruction of the outflow of blood brought about by the pressure of enlarged lymph nodes within the abdomen. In a fifth case, that of a syphilitic subject, the enlarged spleen showed interstitial splenitis. In the 2 remaining cases, microscopic examination of the spleen revealed diffuse hyperplastic changes in the follicles of a sort which suggested a local reaction to the provocative agent responsible for the lymphoid hyperplasia in other parts. In other words, in only 2 cases (12 per cent) was it deemed justifiable to include enlargement of the spleen as a part of the disease lymphosarcomatosis. The clinical value of these findings is significant in view of the fact that it is generally taught that lymphoid splenomegaly is a frequent accompaniment of lymphosarcomatosis.

Pericardium and Heart.—Of the 17 cases of lymphosarcoma in the Bellevue Hospital series, the pericardium was infiltrated in 6 (35 per cent), five times in lymphosarcoma of the thymic remains and once in lymphosarcoma of the anterior mediastinal nodes. In 5 of the 6 cases the penetration of the pericardium was followed by invasion of the heart muscle. In 1 case the right auricle was practically completely replaced by tumor tissue. In a second the growth extended through the right auricular wall and entered the cavity, where it expanded and grew in mushroom fashion. In a third case both auricles were infiltrated, together with the epicardial fat. In another both ventricles were largely replaced, only small sheetlike areas of heart muscle showing at intervals through the tumor infiltrate. In still another case there were a few small nodules in the wall of the left ventricle. In the sixth case the intrapericardial portion of the aorta and the base of the pulmonary artery were studded with tumor nodules and there was a solitary nodule in the wall of the right ventricle, a few small nodules in the wall of the left ventricle and several minute foci in the epicardial fat.

Bronchi, Pleurae and Lungs.—Lymphosarcoma originating in the thymus or its remains or in the mediastinal lymph nodes sometimes molds around the structures of the upper aperture of the thorax, including the trachea, which it may compress, push aside or invade, producing moundlike projections in the lumen. Still more commonly these growths infiltrate and spread through the walls of the larger bronchi for considerable distances and occasionally project into the lumens. In 1 of the 17 cases of the Bellevue Hospital series the growth sur-

rounded a large bronchus in cufflike fashion, replacing the cartilages for a distance of 4 cm.

That the pleura is vulnerable to lymphosarcomatous invasion is illustrated by the fact that in the Bellevue Hospital series of 17 cases it was invaded six times (35 per cent). This is in contrast to the involvement of the pleura in Hodgkin's disease; in 30 necropsies, it was shown to be involved only once. In 1 case of lymphosarcoma both apical pleurae were involved. In 3 cases the visceral pleura of one side was infiltrated throughout, and in 2 of them the diaphragmatic pleura was similarly implicated. In another case the whole of the left parietal pleura was infiltrated. In the remaining case there was a solitary nodule in the pleura of the left side. In 5 of these cases the pleural involvement occurred in association with lymphosarcoma originating in the thorax—in 4 this was thymic lymphosarcoma, and in 1, lymphosarcoma of the mediastinal lymph nodes. The solitary nodule in the sixth case occurred in association with a primary growth of the prostate.

Lymphosarcoma may involve the lung in several different ways. In one group of cases the lung is mechanically compressed by growths arising in the thymus or in neighboring lymph nodes, so that the parenchyma over a variable expanse is almost completely deprived of air. In a second group the peribronchial infiltrate follows the interstitial connective tissues and causes thickening of part of a lobe or of one or more lobes, producing a degree of destruction, which is sometimes further promoted by secondary infection and abscess formation or by putrefaction and gangrene. In a third group the interstitium shows nodular formations which appear to arise in the auxiliary lymphoid foci with which the lung is normally provided. These, too, may become secondarily infected, especially when communication is established between them and the bronchi or the bronchioles, pyrothorax (empyema) sometimes following.

Gastrointestinal Tract.—In the Bellevue Hospital series of 17 cases of lymphosarcoma, involvement of the stomach was not present in a single instance. On the other hand, the growth is encountered with a fair degree of frequency in operations for malignant tumors of the stomach. In such circumstances the nature of the growth is practically never suspected, and the diagnosis is not established until a microscopic examination has been made of the excised tumor or of portions of the tumor removed for biopsy. The growth is almost invariably mistaken for carcinoma.

Prostate.—The prostate normally contains collections of lymphoid cells, which, as a rule, are numerically insignificant and seem to be functionally dormant. However, there are circumstances in which these

cell collections are transformed into lymphosarcoma, usually in patients under 35 years of age. Cases of this description have been recorded by Coupland, Kaufman, Symmers, Quinby and Ferguson and Stewart. The prostate is enlarged in moundlike fashion and may measure 10 cm. or more in its longest diameter. Concomitant growths have been described in the lymph nodes of the pelvis, the abdomen and the groins, together with infiltration of the seminal vesicles, the psoas muscles, the adrenal bodies, the kidneys and ureters, the liver and the pancreas.

SYMMETRIC LYMPHOSARCOMA

According to Fabian, the proclivity of lymphosarcoma to cause symmetric infiltration of tissues is shown in the bilateral involvement of the breasts, the ovaries, the testes, the adrenal capsules and certain paired members of the bony system. One of the most striking of the symmetric infiltrations in patients with lymphosarcoma occurs in the kidneys, in which tumor cells penetrate the connective tissue framework and produce enlargement of the organs without correspondingly extensive or severe microscopic alterations in the tubular epithelium and, apparently, without other than negligible disturbances of the excretory function of the kidney. Lymphosarcoma is not alone in producing changes of the sort described, since an identical lesion is observed in the kidneys in chronic lymphoid leukemia and pseudoleukemia, having, in fact, been mentioned by Cohnheim in his original description of the latter disease. In the 17 necropsies performed at Bellevue Hospital lymphosarcomatous infiltration of the kidneys was encountered three times. In 1 of the cases the kidneys together weighed 1,040 Gm. and each measured 17 by 8.5 by 8 cm. In a second case the kidneys together weighed 1,040 Gm. and each measured 15 by 10 by 7 cm. In both cases the enlargement occurred in association with lymphosarcoma of the thymus. In a third case the kidneys together weighed 630 Gm. and there was an attendant lymphosarcoma of the intestine. In Cohnheim's original case of pseudoleukemia the kidneys were described as "enormously enlarged."

Mikulicz' Disease.—The lymphosarcomatous implication of paired organs is illustrated by a lesion first described by Mikulicz. It usually commences as an infiltrative overgrowth of the lymphoid cells normally existing in the stroma of the lacrimal glands and is signalized by symmetric enlargement of the outer two thirds of each upper eyelid, followed by symmetric enlargement of the parotid and submaxillary glands, likewise due to hyperplasia of preexisting lymphoid collections. Precisely the same combination of symmetric lacrimal, parotid and submaxillary adenopathy has since been described in lymphoid leukemia.

Symmetric Conjunctival Lymphosarcoma.—Bilateral lymphosarcoma of the conjunctival lymphoid tissues came under observation at Bellevue Hospital in a man 37 years of age. The palpebral conjunctiva of the right eye was thrown into folds which caused eversion of the lower lid and encroached on the ocular conjunctiva to the lower level of the cornea. The conjunctiva of the left eye was similarly affected but to a less extent. In addition, microscopic examination revealed lymphosarcomatous infiltration of the tissues of the lower lid.

LYMPHOSARCOMA OF THE LACRIMAL GLAND

Wells and Mayou (1910) recorded a case of lymphosarcoma of the lacrimal gland and collected 11 similar examples from the literature. Frances, Perera and others have since described cases of the same sort. As a rule, the patients are under 38 years of age. The growths are practically always unilateral and tend to infiltrate adjacent tissues.

MYCOSIS FUNGOIDES

According to Fraser (1917), at least nine different views have been advanced to explain the nature of mycosis fungoides: that it is granuloma; a cutaneous form of lymphadenoma (lymphoma); lymphosarcoma; a condition midway between granuloma and sarcoma; an alymphemic type of lymphomatosis; sarcoma engrafted on a previous dermatosis, as psoriasis or eczema; the last phase of a series of dermatoses that includes pityriasis rosea and the parapsoriases; lymphoma of the skin, or, finally, the cutaneous manifestations of a systemic disease.

Mycosis fungoides is a legacy from that era in which clinical features exclusively were depended on as a basis for classification. Later, the use of histologic methods denoted an attempt to emerge from the confusion imposed by the descriptive dermatologist. Unfortunately, these methods were applied to the study of the alterations of the skin alone, in this way providing a heterogeny of histologic changes varying from those of premycosic eruptions to those of tumors and tumor-like lesions of the skin. In more recent times mycosis fungoides has been investigated from the standpoint of the alterations occurring in the deeper parts. On the basis of evidence so adduced it seems to be neither a clinical nor a pathologic entity. In one set of cases the histologic alterations seen in the cutaneous plaques are the same as those in Hodgkin's disease, and the lymph nodes, both superficial and deep, present an identical histologic aspect, while the bone marrow reveals structural alterations that cannot be distinguished from those of Hodgkin's disease. In a second group of cases the tumors of the skin and those of the lymph nodes present the histologic characteristics of lymphosarcoma. Two such cases came under observation at Belle-

vue Hospital. One was that of a woman who showed multiple ulcerative and nonulcerative nodules in the scalp, neck, chest and upper abdominal wall, together with erythematous patches. This case was regarded clinically as one of mycosis fungoides. At necropsy there were innumerable enlarged lymph nodes in the neck and the axillas, around the pancreas and in the mesentery and the pelvis. The spleen was enlarged and weighed 675 Gm. The right psoas muscle was almost completely replaced by infiltrating tumor tissue, and the lower right rectus abdominalis was similarly involved. The right ovary was largely replaced by new growth. In a second case the disarticulated arm of a man contained five or six mushroom-shaped ulcerative lesions in the skin and two nonulcerative nodules, while the muscle tissues of practically the entire extremity were infiltrated by tumor cells. In a third group of cases the histologic changes in the cutaneous tumors and in the lymph nodes are those of lymphosarcoma in which acute leukemic transformation occurs—the so-called leukosarcoma. This designation was used by Sternberg to denote a disease characterized by the presence in some part of the body of a tumor composed of lymphoid cells which are eventually poured into the blood in such numbers as to constitute a form of acute leukemia. Sternberg records 6 cases of lymphoid leukosarcoma, in 4 of which the original growths were located in a part of the mediastinum corresponding to the position of the thymic remains. In 3 of these cases clinical events indicated that the thoracic growths had been present for, respectively, four months, five months and three years. In the fourth case the clinical disturbances were said to have been of three weeks' duration, but the intrathoracic tumor was enormous, and, according to Sternberg, must have been in existence for a period in excess of that suggested by the clinical history. Of the remaining 2 cases of lymphoid leukosarcoma, one was a primary tumor of the orbital region of three months', and the other a tumor of the neck of seven weeks', duration. Cases of mediastinal lymphoid leukosarcoma have been recorded by Weber, Mager, O'Kelly, Cole and others. In a case investigated at Bellevue Hospital the original growth was in the lymphoid tissues of the stomach, and of 2 cases mentioned by MacCallum, one was primary in the breast, the other in the cervix of the uterus.

Kaposi described a condition under the title "lymphodermia perniciosa" in which the changes in the skin were so noticeably like those of mycosis fungoides that the French dermatologists classified it as such. Kaposi's original case was marked by generalized edematous and desquamative eczema with ulcerative cutaneous and subcutaneous tumors made up microscopically of lymphoid cells, by multiple lymphadenopathies and enlargement of the spleen and, near death, by lymphocytosis (white blood cell count, 125,000). At necropsy there were,

in addition, lymphoid nodules in the lungs and diffuse lymphocytic infiltration of the bone marrow. In a case that came under observation at Bellevue Hospital almost identical changes were found.

The patient was a woman who presented a superficially ulcerated tumor in the neck of three years' duration. The mass extended from the occiput into the posterior cervical region. Immediately adjacent were numbers of enlarged lymph nodes, which were matted together. The axillary nodes on the same side were greatly enlarged, a condition which, according to the patient, came on two years after the growth in the neck. The inguinal nodes showed similar involvement, commencing, the patient stated, two months after the axillary enlargement. The skin presented the changes of diffuse exfoliative dermatitis. A dermatologist who saw her made the diagnosis of mycosis fungoides. At the time of the patient's admission the blood showed 15,800 leukocytes. Three weeks before death the white cells numbered 164,000, of which 52 per cent were large mononuclear cells of the lymphocytic type and 14 per cent were small lymphocytes. At necropsy, in addition to the changes mentioned, the tonsils, the anterior mediastinal and peribronchial lymph nodes and the peripancreatic, retroperitoneal and mesenteric nodes were enlarged and numerous. Microscopic examination showed the nodes replaced by diffuse collections of large lymphocytes, together with a few lymphocytes of the small variety. The spleen was similarly infiltrated, and in the perilobular connective tissues of the liver were numerous foci of identical composition. The bone marrow was infiltrated by the same sort of large mononuclear cells, and the blood vessels contained them in numbers.

According to the conception outlined, mycosis fungoides is not a disease entity but a conglomerate of cutaneous changes varying from incidental premycotic eruptions to tumors and tumor-like growths (Symmers, 1932; Berman, 1940). In many cases the premycotic eruptions are absent. When present, according to Sutton, the "earlier manifestations are as capricious in their course as they are variable in their aspect." On the other hand, the tumors and tumor-like growths of the skin are constant and constitute the outstanding feature of the clinical composite. They are attended by the histologic changes of Hodgkin's disease, of lymphosarcoma or of lymphosarcoma with acute lymphoid leukemic transformation. It does not seem possible to reconcile such divergent histologic types with one and the same disease.

SYMPTOMS AND SIGNS

It is obvious that in a disease with such widely diversified anatomic changes as lymphosarcoma the symptoms and signs must be similarly diversified. It may be stated in a general way that in lymphosarcoma symptoms are comparatively few, the disease making its presence known in great measure through objective signs.

DIAGNOSIS

The diagnosis of lymphosarcoma is to be made largely by the process of exclusion in which recourse must be had to blood counts and to biopsy.

PSEUDOLEUKEMIA

Shortly after lymphoid leukemia was discovered independently by Bennett and Virchow, Cohnheim, under the title "pseudoleukemia," described a disease presenting the anatomic characteristics of lymphoid leukemia without corresponding changes in the blood, at least according to the hematologic standards of that day. The patient was a man aged 42, who suffered from anorexia, vomiting and repeated attacks of epistaxis. The leukocytes were considerably diminished in numbers. At necropsy the spleen was increased in size, measuring 25 by 17 by 8 cm., and presented innumerable hyperplastic lymph follicles. The liver was enlarged and on microscopic examination disclosed numerous lymphomatous foci in the perilobular connective tissue. The kidneys were enormous, and the interstitial tissues were richly infiltrated by lymphoid cells. The cervical, inguinal and retroperitoneal lymph nodes were hyperplastic. The gastrointestinal tract presented no noteworthy changes. It is now believed that Cohnheim's original case of pseudoleukemia was in reality one of that variety of lymphoid leukemia in which the white cells are reduced in number and include among them abnormal forms—the so-called aleukemic leukemia or aleukemic myelosis. It is difficult to decide which of the three designations is the most inappropriate. In 1838 Briquet described and illustrated a remarkable lymphoid disease which has since received the equally dubious designation of gastrointestinal pseudoleukemia. It seems to be a clinical and pathologic entity. Although it lacks the infiltrating and destructive qualities of a malignant tumor, it is nevertheless regarded by some as a form of lymphosarcoma. Thus far only 15 cases appear to have been recorded, but the disease is probably commoner than the number of published cases indicates; two well marked examples and a third of comparatively limited proportions have been investigated at necropsy at Bellevue Hospital. Anatomically, the disease is marked by an almost incredible degree of lymphoid hyperplasia extending from the base of the tongue, through the esophagus, stomach and intestine, including the appendix, to the anus, occurring oftenest in the form of closely packed nodules, most numerous in the stomach and intestine and varying in diameter from 1 to 5 mm. but sometimes projecting as polypoid masses measuring several centimeters in height. Peyer's patches are often hyperplastic to an extreme degree, occasionally ulcerated. The spleen is practically always greatly enlarged, as are the lymph nodes of the abdomen and the chest. The superficial nodes in various localities are apt to participate to an almost equally remarkable extent. In a review of the literature Wells and Maver were able to collect reports of 7 cases of gastrointestinal pseudoleukemia in which the changes in the lymphoid tissues were no less remarkable than those just described. They added another case and Symmers, Hoffman, Celler and Shoemaker have each recorded a case since then.

SYMPTOMS AND SIGNS

In spite of the extensive changes in gastrointestinal pseudoleukemia, clinical symptoms referable to them are surprisingly few and consist of diarrhea alternating with constipation, sometimes bloody stools, occasionally intussusception, and emaciation. There are no specific changes in the blood.

TREATMENT

Radiation is the accepted method of treating pseudoleukemia.

SUMMARY

The lymphoid diseases are five in number and include Hodgkin's granuloma, giant follicular lymphadenopathy, lymphoid leukemia, lymphosarcoma and gastrointestinal pseudoleukemia. All of them are initiated by hyperplasia of lymph follicles. In the majority of cases they are preponderant or, if one prefers the term, "primary" diseases of the deeper lymphoid structures, including the abdominal lymph nodes or the abdominal and thoracic nodes, combined, the spleen, the thymus and the gastrointestinal tract. Enlargement of the superficial nodes, if it occurs at all, is seldom preponderant or "primary" but is a late sequence.

According to one view (Symmers), the histogenesis of Hodgkin's disease is determined by myeloidization of the lymph nodes, the spleen and other lymphoid structures brought about by embolism due to deposition of cells derived from the bone marrow—megakaryocytes, nongranular mononuclear giant cells or hemocytoblasts, eosinophils and eosinophilic myelocytes. According to another view (Mallory), Hodgkin's disease is a primary malignant tumor of the lymph nodes, or lymphoblastoma; still other opinion holds that it is a primary malignant tumor of the bone marrow composed of megakaryocytoblasts, which metastasize to lymphoid tissues (Medlar).

Giant follicular lymphadenopathy is characterized by numerical and dimensional hyperplasia of lymph follicles and in this respect may retain its individuality from beginning to end. In other instances it may be transformed into polymorphous cell follicular sarcoma or into Hodgkin's disease or into lymphoid leukemia. One of the most significant and encouraging features of giant follicular lymphadenopathy is its amenability to radiation therapy, considerable numbers of patients who were treated by this method having remained apparently well for periods varying from three to fourteen years.

Cases of chronic lymphoid leukemia are divisible into two groups. In one group the lymph nodes are preponderantly or primarily enlarged in contradistinction to the size of the spleen, which may be normal or only slightly or moderately enlarged. In the second group this order

is reversed, the spleen attaining massive proportions while the lymph nodes remain relatively small.

It is defensible to consider the possibility that so-called lymphosarcoma of dogs is caused by a virus of exalted virulence, suggested by the fact that the lesion is easily reproduced both by natural and by artificial means. It is equally defensible to consider the possibility that lymphosarcoma of man is caused by a virus that is transmissible to one of the same species, though the degree of infectivity is low and the method of transmission of the virus is effectively concealed. Cases of human lymphosarcoma are divisible into five groups: one, cases characterized by involvement of paired organs; a second, cases in which regional collections of superficial lymph nodes are involved; a third, cases in which the lymphoid structures of the thorax, especially the thymus or its remains, are implicated; a fourth, cases of Sternberg's leukosarcoma, in which lymphoid tumors occur in various situations and eventually pour their lymphocytes into the blood in such numbers as to terminate life by acute lymphoid leukemia; and, a fifth, comprising the most frequent cases of all, in which the lymphoid tissues of the abdomen are involved, including the stomach, the intestines and the retroperitoneal and mesenteric lymph nodes.

Under the title "pseudoleukemia," Cohnheim described a disease presenting the anatomic characteristics of chronic lymphoid leukemia without changes in the blood, at least according to the hematologic standards of that day. It is now believed that Cohnheim's case was one of so-called aleukemic myelosis, in which the white cells are reduced in number and include abnormal forms. Briquet described a remarkable disease which has since received the dubious designation "gastrointestinal pseudoleukemia." Although it lacks the infiltrating and destructive qualities of a malignant tumor, it is nevertheless regarded by some as a form of lymphosarcoma. The disease is marked by an almost incredible degree of lymphoid hyperplasia extending from the base of the tongue, through the esophagus, stomach and intestine, including the appendix, to the anus. The spleen is practically always greatly enlarged, as are the lymph nodes of the abdomen and the chest. The superficial nodes in various localities are apt to participate to an almost equally remarkable extent.

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Notes and News

Appointments, Etc.—Alfred Golden has resigned as director of the laboratories of the Baptist Memorial Hospital, Memphis, Tenn., and assumed the associate professorship of pathology in the University of Tennessee.

Wendell M. Stanley has been appointed to direct a new laboratory for virus research at the University of California. Dr. Stanley, 43, heads a virus laboratory for the Rockefeller Institute for Medical Research at Princeton, N. J. He received the Nobel prize in 1946 for his work on viruses.

Bernhard Steinberg, pathologist and director of laboratories at the Toledo Hospital, and director of the Toledo Hospital Institute of Medical Research, will now devote his entire time to the institute, which is endowed. Investigations of the production and the distribution of leukocytes and platelets are conducted. Problems of glaucoma are also being investigated under a grant from the Snyder Ophthalmic Foundation.

Society News.—The American College of Physicians announces the awarding of six research fellowships in medicine for the year beginning with July 1948. The purpose of these fellowships is to give young physicians preparing for an academic career in internal medicine or in pediatrics an opportunity of a year of investigative experience as an early part of their preparation. Similar fellowships will be awarded for the year beginning with July 1949.

The 1948 annual meeting of the American Institute of Chemists will be held Saturday, May 8, 1948, at the Hotel Pennsylvania, New York. The program will commemorate the silver anniversary of the institute, which was founded in New York in 1923.

The American Association for the Advancement of Science will celebrate the hundredth anniversary of its founding by a meeting to be held in Washington from Sept. 13 to Sept. 17, inclusive, 1948.

Awards.—Ida A. Bengtson, retired senior bacteriologist of the National Institute of Health, was recently awarded the medal of the United States Typhus Commission in recognition of the contribution which she made to the control of typhus fever during World War II.

Virus Diagnostic Laboratory.—The Public Health Research Institute of the City of New York, Inc., is organizing for the health department a service designed to insure the diagnosis of viral and rickettsial diseases. The laboratory will be headed by George K. Hirst, chief of the division of infectious diseases of the institute. When the laboratory is ready, practitioners will be able to go to the health department for the advice of virus disease specialists.

International Poliomyelitis Conference.—The National Foundation for Infantile Paralysis will hold its first international conference on poliomyelitis in the Waldorf-Astoria Hotel, New York, July 12-17, 1948. More than sixty foreign countries will be represented. There will be a scientific exhibit. The executive secretary of the conference is Stanley E. Henwood, with headquarters at the Waldorf-Astoria Hotel.

Fellowships for Teachers of the Pathology of Tumors.—Through the W. T. Grant Foundation there are available in the laboratories of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, certain fellowships respecting the pathology of tumors. The fellowships may be held by suitably qualified persons interested in the teaching of pathology. Requirements are that the candidate shall hold appointment as assistant professor or instructor in a university department of pathology and that he shall be given leave to be absent for one year with a guarantee that he may return to academic status, preferably

in the same department of the university, after completion of the fellowship. These fellowships are designed mainly for training and especially for training of personnel of universities which have received government grants-in-aid for the establishment of correlated work in the teaching of cancerology. Holders of the fellowships will have access to approximately 18,000 specimens per year and will be expected to attend conferences and follow-up clinics for the purpose of acquiring familiarity with the behavior of cancer as observed in living patients and as correlated with laboratory observations. Research may be undertaken as a minor portion of the program, provided it forms a part of one of the research programs being conducted in the institution. The annual stipend is $5,000, an amount which is considered exempt from federal income tax. The university may supplement the stipend if it deems this necessary in any individual case. A fellowship may begin at any time.

Application should be made to Dr. Fred W. Stewart, Memorial Hospital, 444 East Sixty-Eighth Street, New York 21.

Deaths.—A. H. Roffo, director of Instituto de Cancerologia, Universidad de Buenos Aires, died July 23 last.

F. Parker, assistant professor of pathology at the University of Virginia, died of a heart attack on December 1 at the age of 41.

F. E. Sondern, clinical pathologist, died October 10 last at the age of 80.

Appointments.—J. A. Baker, of the department of animal and plant diseases of the Rockefeller Institute for Medical Research, has been appointed professor in the department of pathology and bacteriology of the New York Veterinary College.

Domingo Brachetto-Brian has been appointed director of the Instituto de Cancerologia, Universidad de Buenos Aires, in succession to the late A. H. Roffo.

The Life Insurance Medical Research Fund.—Up to Jan. 15, 1948, applications will be received for grants-in-aid of research on cardiovascular problems to begin in 1948. Support is available for physiologic, biochemical and pathologic research which bears on cardiovascular problems, as well as for clinical investigation in this field. About $500,000 will be awarded for these grants.

Postgraduate fellowships for training in research for 1948-1949 are also available, and applications will be received for these up to Jan. 1, 1948. Preference will be given to candidates wishing to work in the broad field of cardiovascular function or disease and to those wishing to work in institutions other than the ones where they obtained most of their experience. The degree of Ph.D. or M.D. or the equivalent is required. About twelve fellowships will be available with annual stipends of $2,500 to $3,500.

Later in the year, the Fund will also offer a number of predoctoral research fellowships. Further information may be obtained from the Scientific Director, Life Insurance Medical Research Fund, 2 East 103d Street, New York 29.

Merck Fellowships.—The National Research Council has announced that the Merck Fellowships, supported by Merck & Co., Inc., and administered by the Council, are available for the academic year 1948-1949. This program, designed to stimulate interest in fields of study requiring knowledge of more than one science, offers fellowships to provide special training to young men and women who have demonstrated marked ability in research in chemical or biologic science and who wish to broaden their fields of investigational activity. Candidates must submit evidence of training in these fields equivalent to that represented by the degree of Ph.D. and must have demonstrated unusual research ability. Study abroad may be approved in some cases. The annual stipends are $2,500-$5,000, and an annual allowance of $500 is made to the institution to which each fellow is assigned. Fields of study will be in chemistry and biology, including preclinical medical sciences.

Books Received

THE SELECTED WRITINGS OF BENJAMIN RUSH. Edited by Dagobert D. Runes. Pp. 433. Price $5. New York: Philosophical Library, 1947.

The selections include writings by Benjamin Rush on good government, on education, on natural and medical sciences and on miscellaneous topics, with a list of his writings, published during his life, and a selected bibliography about him. Benjamin Rush, 1745-1813, signer of the Declaration of Independence, was a great physician—easily the ablest American clinician of his time. He was also a naturalist and a champion of social and political freedom. The book will interest students of the medical and social conditions of his time and of his efforts to improve them.

NUTRITION IN RELATION TO CANCER. By Charles Glenn King and others. Price $2. New York: The New York Academy of Sciences, 1947.

One number of the *Annals of the New York Academy of Sciences* (**49**:1-140 [Sept. 7] 1947) contains eleven short reviews which were presented at a conference sponsored by the New York Academy of Science and the Panel on Nutrition, Committee on Growth, National Research Council, on Dec. 6 and 7, 1946. Six of these papers deal with nutrition, and the remaining five are concerned, respectively, with the milk agent in mammary cancer, tumors of plants, chemically induced mutations, nutrition of monocellular animal organisms, and nutrition of cancerous tissue in vitro. The articles are authoritative, and some contain material not readily available elsewhere. They all give references, and some are illustrated. This is a worthy addition to the literature of cancer.